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CEREBRAL ARTERIAL SPASM SUBSEQUENT TO DEFINITE SUBARACHNOID HEMORRHAGE IN HUMANS

by

© Ronald E. Hyndman, M.D.

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE

OF MASTER OF SCIENCE (SURGERY)

Faculty of Medicine

Department of Surgery

EDMONTON, ALBERTA

FALL, 1969

THE UNIVERSITY OF ALBERTA

CEREBRAL ARTERIAL SPASM SECONDARY TO INDUCED SUBARACHNOID HEMORRHAGE IN MONKEYS

by

© Ramon R. Erasmo, M.D.

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Cerebral Arterial Spasm Secondary to Induced Subarachnoid Hemorrhage in Monkeys" submitted by Ramon R. Erasmo in partial fulfilment of the requirements for the degree of Master of Science (Surgery).

DEDICATED

to

The late THOMAS J. SPEAKMAN, M.Sc., M.D., F.R.C.S.(C)

Clinical Professor, Division of Neurosurgery

The University of Alberta

Edmonton, Alberta, Canada

ABSTRACT

A method of studying cerebral arterial response to induced subarachnoid hemorrhage has been developed in rhesus monkeys. Induction of subarachnoid hemorrhage was accomplished by injecting fresh autogenous arterial blood through a needle inserted via a twist drill hole placed half a centimeter superior to the nasion. Introduction of the needle was guided radiographically into a midline about half a centimeter anterior to the tuberculum sella. Injection of the blood at this area of the subarachnoid space was effective in allowing blood to come into contact with the two observed arteries.

These moderately separated tributaries of the anterior portion of the Circle of Willis were studied. The supraclinoid segment of the right internal carotid and the proximal segment of pericallosal arteries were observed during weekly inductions of subarachnoid hemorrhage.

Cerebral arterial spasm was statistically proven to occur in each of the three weeks of experimentation. The vasospasm produced did not last for a week, nor was it increased by repeated weekly blood injections. The degree of vasospasm did not differ between the two observed arteries over the three weeks. Six experimental variables were measured and found not to influence significantly this vasospastic response.

ACKNOWLEDGEMENTS

Dr. Bryce K.A. Weir, my project supervisor, for his constant guidance and unremitting encouragement.

Dr. Jack D.R. Miller, who took charge of all radiologic procedures.

Dr. John McIntyre and Dr. Donald Dobson, who handled all the surgical anesthetic requirements.

Dr. Bruce Mielke, who took charge of all post mortem examinations.

Dr. Thomas Overton, who directed all the radioisotopic studies.

Dr. David Secord and Mr. Morris Trach, who took charge of the veterinary care of the experimental animals.

Mr. Clarke Hazlett, for his assistance in the statistical analysis.

Miss Darlene Munawich, for typing.

This work was supported in part by a Medical Research Council Grant to Dr. Bryce K.A. Weir. A Neurosurgical Research Fund of The University of Alberta Hospital was also used in this project.

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CHAPTER I

INTRODUCTION

INTRODUCTION

The concept of cerebral arterial spasm playing a major role in transitory neurologic phenomena such as migraine, aphasia, epilepsy, temporary hemiplegia and hypesthesias, has been suggested on an empirical basis by investigators since the middle of the nineteenth century.

Brunton [11,12] was among the first to hypothesize functional disturbances in cerebral arteries. Du-Bois-Reymond in 1868 attributed the visual phenomenon of migraine and epileptic convulsions to diminution of cerebral blood pressure caused by the contraction of arteries.

Since then, cerebral vasospasm has been mentioned frequently in association with a variety of clinical conditions ranging from hypertensive hemorrhagic apoplexy [16] to ruptured intracranial aneurysms. Actual occurrence of vasospasm was originally questioned by Pickering [86] who stated that true spasm was rare. This brought out differences of opinion as to what constituted vasospasm as opposed to vasoconstriction. Vasospasm has been described as an involuntary and excessive contraction of muscle fibers in the vascular wall. In essence it has been regarded as a pathologic process. Potter [92] described physiologic vasoconstriction of arteries as an even and rather diffuse process in contradistinction to vasospasm, which was neither. Both vasoconstriction and vasospasm are active processes depending on the properties of the smooth muscle. Roy and Sherrington [101] described another process in which passive reduction of the caliber of cerebral arteries occurs when intra-arterial pressure falls. In this thesis vasoconstriction and vasospasm are regarded as synonymous.

Since it was first recognized that cerebral arteries are capable

of constriction, numerous investigations have been carried out using various mechanical and chemical stimuli. By the time the first radiologic evidence of vasospasm was presented, many clinical conditions had already been postulated to be caused by or at least associated with it. The technique of cerebral angiography and related diagnostic procedures has improved considerably since its introduction. It is now possible to determine whether vasospasm is occurring and also its degree and distribution. This direct demonstration of vasospasm with other evidence permits speculation regarding etiology. Associated physiological and biochemical alterations can also be measured. The presence of cerebral vasospasm in response to various stimuli has been relatively easy to demonstrate, but the precise mechanism of production has escaped full understanding. The precise sequence of events leading to its production is still unknown.

Studies directed toward elucidating the anatomical structure of the cerebral arteries revealed no significant difference between comparable arteries in other parts of the body. What was obviously noted was the uniqueness of their surrounding medium. The arteries at the base of the brain are bathed with cerebrospinal fluid and are almost devoid of supporting connective tissue. In subarachnoid hemorrhage (SAH) the Circle of Willis and its branches are in direct contact with blood and subsequently the products of its decomposition.

The complete innervation of the cerebral arteries has not been fully demonstrated. A neurogenic etiology in the production of cerebral vasospasm has been almost but not completely discounted. Results of experimental studies on the identifiable nerve supply of the cerebral arteries has not been sufficient to explain the degree, distribution and duration of vasospasm seen clinically. Stimulation of the sympathetic

innervation of the basal arteries revealed an unremarkable response, ranging from no response at all to 8 - 10% vasoconstriction [36,37].

Much recent work has been directed to analysing the response of the arterial wall to local physical and chemical change. Clinical evidence has accumulated to confirm the close association between cerebral vasospasm and intracranial aneurysmal rupture producing subarachnoid hemorrhage. This condition produces a local physical distortion in the arterial wall and simultaneously changes its chemical surrounding with extravasated blood.

Blood and its decomposition products were the next targets of experimental scrutiny. Vasoactive substances including those which are normally circulating and those released at the time of the hemorrhage have been shown to alter the caliber of cerebral arteries to a variable extent and duration. None, however, has been experimentally proven to produce a response analogous to the typical clinical condition.

Other components of blood, like serum electrolytes and blood gases, have been considered in the pathogenesis of cerebral vasospasm. Investigative results are still conflicting. There has been indication that the presence or absence of certain electrolytes and changes from normal of certain blood gases could affect the cerebral arterial response to a particular experimental stimulus.

As demonstration of cerebral vasospasm became precise, more significant correlations were made to clinical conditions. With diminution of arterial caliber, it becomes obvious that certain hemodynamic changes occur in the blood supply to the brain. This presumably results in different degrees of neurological deficits under certain conditions.

The problem has been compounded in the case of subarachnoid hemorrhage resulting from the rupture of intracranial aneurysms. This

is a situation which frequently produces vasospasm. The direct surgical treatment of aneurysms could possibly produce or perpetuate this pathological vascular response.

The necessity of clearly defining the pathogenesis of cerebral vasospasm is obvious. The logical approach to its treatment depends upon the full understanding of its nature.

CHAPTER II

THE PRESENT PROBLEM AND HYPOTHESIS

THE PRESENT PROBLEM AND HYPOTHESIS

Various experimental methods have been developed in the past to study the cerebral arterial response to blood and its breakdown products. A great number of these investigations employed a direct approach to the problem. This frequently involved major surgical procedures before actual observations were made. Various investigators have made use of extensive craniotomies and transoral or transclival approaches to expose particular cerebral vessels. These have been quite satisfactory, in answering particular problems. They had the advantage of direct visual observation of changes in the cerebral blood vessels, without resorting to less accurate indirect methods. However, there are limitations in correlating these findings with clinical situations. In this respect these earlier methods had some drawbacks in that major experimental variables were added to the effect of SAH.

In the present study, a method of indirect observation was proposed. This was developed by taking into consideration common existing clinical conditions, of which SAH secondary to ruptured aneurysm of the anterior portion of the Circle of Willis is most frequent. No major surgical trauma, which might have interfered with the simulated clinical condition, was induced. Physiological conditions were maintained as closely as possible to normal.

The present study was commenced with the hypotheses that:

A. Fresh autogenous arterial blood, when introduced into the subarachnoid space in the vicinity of an intact supraclinoid segment of right internal carotid and proximal segment of pericallosal arteries, produces vasospasm within the first five to ten minutes of introduction.

B. Repeated injections of fresh autogenous arterial blood at weekly intervals produces similar degrees of vasospastic responses from each of the two arteries.

C. The degree of vasospastic response to subarachnoid blood is the same for both arteries over the three weeks of experimentation.

CHAPTER III

REVIEW OF LITERATURE

REVIEW OF LITERATURE

1. Evidence of Cerebral Vasospasm.

The capacity of the cerebral arteries to go into spasm has been shown in experimental animals by the application of various physical stimuli. This was shown in the works of Florey, 1925; Riser, 1931; Villaret and Cachera, 1939; Echlin, 1942; Harvey and Rasmussen, 1951; Byrom, 1954; Pool, Jacobson and Fletcher, 1958; Lende, 1960; and Raynor and Ross, 1960. Manipulation of the Circle of Willis and its branches in man in surgical procedures produced similar vasospastic responses (Bassett, 1951; Pool, Jacobson and Fletcher, 1958; Gillingham, 1958; Gurdjian and Thomas, 1959; Krayenbuhl, 1960; Potter, 1961).

The first arteriographic evidence of cerebral vasospasm was reported in 1950 by Reid, Johnson and Ollerenshaw, during the Sixth International Congress of Radiology in London. The cerebral arteriogram showed vasospasm associated with subarachnoid hemorrhage secondary to a ruptured berry aneurysm. Subsequent reports describing a similar phenomenon were made by Ecker and Riemenschneider, 1951; Johnson et al., 1958; Pool et al., 1958; and Fletcher et al., 1959.

It has been suggested that vasospasm is an optical illusion, attributable to physical phenomena such as laminar flow of contrast material [1]. This was easily ruled out by taking radiographs in several projections.

To avoid misinterpretations of arteriograms, several pertinent points were brought up by various investigators which serve as criteria for the diagnosis of cerebral arterial spasm. One of the foremost distinguishing characteristics of vasospasm is that the localized narrowing

of the arteries seen in the first arteriogram should have disappeared in subsequent ones. Fletcher et al. [34] defined spasm as a narrowing of the lumen of the vessel beyond that which is considered a normal anatomical variant. The narrowing almost exclusively involves the intracranial arteries. The cervical arteries are rarely affected. In arteries, where different segments normally have relatively constant diameters, certain guide lines have been established to diagnose vasospasm. This is exemplified in the case of the supraclinoid portion of the carotid artery, whose diameter is two-thirds or more of the intracavernous portion. Vasospasm is not considered significant unless its diameter is less than two-thirds of the intracavernous portion. In certain arteries exhibiting variations from normal, like a hypoplastic anterior cerebral artery, the narrowing is not considered as vasospasm unless a local segment only is involved [34].

Other salient features [92] that characterize this pathologic state of cerebral vasospasm include the following:

A. Spasm is confined to intradural vessels with few exceptions.

B. It is essentially proximal, always near the Circle of Willis, frequently involving the terminal part of the carotid artery, but sparing the more distal branches which may be larger in caliber than the carotid artery itself.

C. It may be proximal or distal to the ruptured aneurysm, less frequently on the opposite side. Occasionally it is remote from the aneurysm, as in a case of severe bilateral internal carotid arterial spasm after rupture of an aneurysm at the origin of the posterior inferior cerebellar artery.

D. It is often patchy and irregular, and the length of involved segment varies considerably.

E. There is usually a slowing in the affected part of the cerebral circulation as judged from the timing of the angiograms.

F. The narrowing may persist for several weeks.

G. Vasospasm usually does not occur in arteries showing clear-cut evidence of arteriosclerotic changes. Its incidence falls sharply in patients over the age of fifty, as noted by Fletcher et al. [34].

Sources of error in the interpretation of cerebral vasospasm from arteriograms were recognized as early as 1951, a year after its first demonstration. Important differential factors include the following:

A. In an artery congenitally narrowed, or narrowed by an atheroma, repeated arteriograms may show no change of caliber of the same artery.

B. Narrowing of an artery due to longitudinal stretching by local brain swelling or hematoma is usually even. This is usually temporary. It could be permanent, if the vessel is stretched over an aneurysm filled with laminated thrombus which is not demonstrated in its entirety.

C. Pseudospasm [28] results from variation of blood flow causing non-filling or partial filling of the lumen of the artery. This has been attributed to changes in intra-arterial pressure in the carotid artery distal to the site of injection of contrast material. During the injection of contrast material there is a slight increase, followed by a slight decrease in pressure after injection. This is thought to be caused by the mere presence of the needle in the artery causing slight obstruction, or spasm of the arterial wall due to the puncture or sub-intimal hematoma. All these factors tend to change the direction of blood flow, from the contralateral carotid artery through the anterior communicating artery and from the basilar artery through the posterior communicating artery, towards the injected side. This appearance of pseudospasm could be due entirely to a slight delay in exposure of the

arteriogram.

D. The streamlined nature of the flow of blood could cause the contrast material to occupy only certain laminae occupying only a part of the actual lumen of the artery.

Fletcher et al. [34] categorized cerebral vasospasm into local and diffuse. The former is characterized by constriction of an area in the blood vessel 1 to 2 cm. proximal or distal to the aneurysm. Zingesser et al. [128] proposed the same classification, and went further by dividing the severity of spasm into three groups, although none of those they first classified had premorbid arteriograms for comparison.

Grade I - the caliber of the blood vessel involved is narrowed by less than 50%.

Grade II - the caliber of the vessel involved is narrowed by more than 50%.

Grade III - the change in the caliber of the vessel involved is barely visible.

2. Correlative Anatomy.

The anatomy of the gross blood vessels of the brain is well known and will not be described here. Only those aspects which relate to the study will be reviewed.

Congenital anomalies of the Circle of Willis, especially those of the anterior and posterior communicating arteries, should be taken into consideration while interpreting arteriograms in relation to vasospasm.

The concept of true end or terminal arteries of the brain has been questioned strongly. The microcirculatory system in the cerebrum and cerebellum in man and in dogs contains pre-capillary "thoroughfare channels" which also exist in other organs of the body. Arteriovenous anastomoses with diameters of 14μ to 25μ have been demonstrated in the

subcortical white matter [29,49,80].

It is well established that there is no essential difference between the anatomic characteristics of cerebral arteries and most of the other arteries of the body of the same size, as had been originally suggested [88]. They have an adventitia, vasa vasorum, elastica, muscularis, intima, and both myelinated and non-myelinated nerve fibers, all of which gradually become less prominent as the diameter of the blood vessel decreases.

The main innervation of the major cerebral arteries is said to arise from the pericarotid plexus, upper cervical roots and the tympanic plexus. Fibers from the vagus and upper two cervical roots are believed to supply the vertebral and basilar arteries. Branches from the third, fifth, seventh, ninth, eleventh and twelfth cranial nerves are also said to contribute fibers to the cerebral arteries [88]. It has been suggested that the Circle of Willis is supplied by afferent fibers through the ipsilateral trigeminal nerve [96], vasodilator fibers via the facial nerve [19], vasoconstrictor fibers from the cervical sympathetic system [10,71] and fibers capable of vasoconstriction directly from the brain stem or by way of the ninth, eleventh or twelfth nerves.

Intrinsic axonal reflex mechanism should also be considered in the local vasomotor activity of the arteries [88].

Electron microscope observations on the human intracranial arteries [23] confirmed the existence of the following:

A. Myelinated and non-myelinated fibers within the adventitia of relatively large cerebral blood vessels.

B. Efferent and presumably adrenergic nerve endings containing vesicles with osmophilic centers.

C. Structures that resemble digital tactile organs that may represent

afferent terminals.

D. No specific nerve endings in the tunica media or tunica intima.

X-ray microscopic study of the intracranial arteries using the Corlett Nixon X-ray projection microscope [23] showed that there were no vasa vasorum in the arterial walls of the Circle of Willis distal to the origin of the anterior, middle and posterior cerebral arteries, which suggests a luminal source of nutrition. Intracranial arterial supply of the vertebral, basilar and internal carotid arteries were formed by extensions of the extracranial adventitial plexus. The arterial vasa originated extramurally as branches of the parent artery which looped back and were distributed to the adventitia.

The anatomical location of cerebral arteries was observed to be related to the responses to various experimental stimuli. The responses to similar stimuli by comparable arteries were shown also to vary with the type of species.

Gurdjian et al. [45] claimed that pial vessels over the cerebral convexities of monkeys do not respond to mechanical stimuli. On the other hand, the larger vessels of the Circle of Willis of the same animal contract vigorously with similar stimuli [21,48,88,90,98]. In contradistinction, the pial arteries over the cerebral convexities of cats and dogs are highly and moderately reactive respectively [26,120].

The anatomic differences in the blood supply to the brain between man and monkey have been noted by Bonakdarpour et al. [7]. This is of importance because a number of experimental investigations are carried out with these animals. The present study used monkeys. The chief differences lie in the fact that both common carotid arteries in monkeys arise from the brachiocephalic artery and the anterior cerebral arteries unite to form a single pericallosal trunk.

The anatomic location of the aneurysm may be related to the likelihood of vasospasm. Maspes et al. [78] claimed that the highest probability of vasospasm was with aneurysms situated at the carotid bifurcation (60%). This was followed in order by those of the anterior communicating (43%), posterior communicating (32%), anterior and middle cerebral arteries with equal percentage (30%) and the first portion of the supraclinoid syphon (23%). Allcock et al. [1] and Schneck et al. [105] each gave somewhat different figures. It appears that there is no unanimity of opinion on this particular aspect. Wilkins et al. [122] showed that the frequency of vasospasm was slightly less in association with vertebrobasilar aneurysms than with aneurysms at other sites.

3. Pathogenesis of Cerebral Vasospasm.

There has been much conjecture as to the precise mechanism by which cerebral vasospasm is brought about. At one time, it was claimed that the contrast material used in the arteriograms could be a predisposing and/or perpetuating factor [44,54,98], but this has been disputed by other investigators who substituted non-irritating substances as contrast material in their studies [1,53].

Since the first use of the Forbes Window [36] for direct observation of cerebral vessels, numerous investigators have used it to study the effects of the direct stimuli on the cerebral vessels. Florey [35] described the effects of mechanical and electrical stimuli on pial vessels over the cerebral convexities of cats. Echlin confirmed the above observations but studied larger vessels [25,26]. Pool observed similar effects in man. Harvey and Rasmussen [48], Pool [88], Pool et al. [90], Raynor and Ross [98] and Corday et al. [21] described vigorous contraction of the larger vessels of the Circle of Willis in cats and monkeys on mechanical stimulation. Gillingham [39], Penfield et al. [85],

Ecker and Riemenschneider [28], Botterell et al. [8], Johnson et al. [60] and Pool et al. [90] observed similar effects in man.

In recent years, with the refinement of techniques for cerebral angiography evidence has accumulated associating vasospasm (particularly of the larger arteries of the brain) and subarachnoid hemorrhage from ruptured aneurysms [1,24,28,34,60,78,88,92,93,105,123].

Some postulated causes of vasospasm in intracranial arteries are as follows:

A. Byrom [16], based on Bayliss' observations, contended that cerebral arteries responded by constriction to a sudden direct increase in intra-arterial pressure. This was criticized because it was noted that Bayliss' observations did not include cerebral arteries [92].

B. Spasm secondary to mechanical stimulation has been shown by Echlin [26] and Lende [76] to be independent of the sympathetic nervous system and mediated largely by vascular musculature.

C. Pool [88] suggested that a neurogenic factor is also involved in the process, but Forbes et al. [36,37] claimed that cerebral blood vessels constrict only by 8 to 10% on stimulation of the cervical sympathetic nerves.

D. Johnson et al. [60] considered physical stretching or pulling on subarachnoid bands by the blood in the subarachnoid space as a cause of vasospasm. They added that narrowing could be accentuated by distortion and rotation caused by the twisting of the aneurysm as it bleeds.

E. Extravasated blood and its subsequent breakdown products alone or in combination with mechanical factors [9,27,63,65,73,83,85,117,124] have been the subject of investigation as a major causative agent. Among other substances in the blood, serotonin has been considered as a likely factor [13,64,65,66,69,97,104,117,123,124].

4. Clinical Implications of Cerebral Vasospasm.

With the occurrence of vasospasm, hemodynamic changes result in the area supplied by the affected vessel. The importance of blood pressure gradient to satisfactory tissue perfusion is well known. Its relationship to blood flow is a simple one. On the other hand, the brain has an intrinsic mechanism to maintain a constant flow in the face of changing pressure. Cerebral blood vessels have the ability to vary their diameters and consequently peripheral resistance in order to preserve a constant blood flow. This "autoregulation" is independent of nervous control [18,68,75,119].

In the case of pathologic vasospasm, the intrinsic and extrinsic controlling factors appear to be altered since adequate tissue perfusion may not be maintained. What remains to be clarified is the effect of the diminished caliber of the larger arteries on the cerebral blood flow. If Poiseuille's Law were applicable, the volumetric rate of blood flow to an area would then vary with the fourth power of the diameter of the supply vessel. It seems unlikely that this relationship can be applied directly in cerebral pathophysiology.

Using radioactive isotopes, Hedlund (1965) calculated the cerebral blood flow to be 915 ml./min. as measured in twenty-five healthy men between the ages of 25 and 50 years. This figure is similar to that reported by Kety et al., in a Public Health Report in 1963. They estimated cerebral blood flow to be 62.1 ml./min./100 gm. of brain substance, which is equivalent to 930 ml./min. for a 1,500 gm. brain. Slightly lesser values were reported by Bernsmeier and Siemons (1953), with corresponding figures of 58 ml./min./100 gm., which is 870 ml./min. In the case of a cerebral artery affected with vasospasm, if Poiseuille's Law applies, a reduction of blood flow of 25-fold to 400-fold has been

estimated to occur [93].

If such a drastic reduction in flow occurs, some other channels may open into the area supplied by the spastic arteries. If the vasospasm is occurring in the carotid arterial system, the vertebro-basilar system might be required to transmit an enormous excess of blood to compensate for the deficit in the anterior circulation. It has been shown that the basilar artery is capable of doing so, with relatively slight degree of dilation [93].

Potter [93] has presented some evidence that there is redistribution of blood from the posterior circulation to the areas supplied by spastic vessels of the carotid system. Since it was shown that the posterior communicating artery was not significantly involved in this redistribution, it was suggested that the leptomeningeal anastomotic channels are the main pathways to the fringes of the carotid territory [58,93].

All these compensatory mechanisms, aimed to restore normal circulation in the face of vasospasm, have not been satisfactorily proven to be effective either clinically or experimentally. However, if they were, morbid states could then be theoretically expected to occur if compensatory redistribution failed to occur. Robertson [99] concluded that ischemic lesions in patients with ruptured aneurysms were occasionally due to arterial spasm and that "it is probable that this mechanism is far commoner than realized". Norlen and Olivecrona [82] pointed out the presence of vasoconstriction shortly after hemorrhage from ruptured aneurysm and considered this vasoconstriction to be a protective mechanism to prevent further hemorrhage. Fletcher et al. [34] claimed that hemiplegia, coma, aphasia and other signs of neurologic deficit could result from impairment of circulation secondary to spasm. Logue [77] offered

similar conclusions. Botterell et al. [8] pointed out that vasospasm may result in hypoxia of the brain stem and produce serious if not fatal cerebral edema. Hunt et al. [57] also partly attributed the diffuse ischemic damage of the brain to vasospasm. Pool [89] indicated the influence of vasospasm in the postoperative results in patients with subarachnoid hemorrhage secondary to ruptured intracranial aneurysm. Allcock et al. [1] considered arterial spasm as the main cause of postoperative morbidity and mortality in patients with subarachnoid hemorrhage and ruptured intracranial aneurysm. Stornelli et al. [116] offered similar views by concluding that "diffuse intracranial vasospasm is a principal concomitant of fatality in patients with subarachnoid hemorrhage". Zingesser et al. [128], using an inert diffusible indicator in their study of cerebral blood flow, claimed there was a depression of general flow in patients with subarachnoid hemorrhage. A poor correlation was obtained between regional blood flow and the presence or absence of vasospasm. Patchy ischemia of the cortex and edema of the white mater, maximal in the territory supplied by the aneurysm-bearing vessel, but present throughout the cerebral hemispheres, were observed by Smith [15,112]. She attributed these changes primarily to vasospasm.

CHAPTER IV

MATERIALS AND EXPERIMENTAL PROCEDURES

MATERIALS AND EXPERIMENTAL PROCEDURES

A total of 6 rhesus monkeys were used in this experiment. All were female and varied in weight from 2.7 to 6.9 kg. They were originally imported from India. Each of these monkeys was subjected to a conditioning period of about 56 days by the importing firm prior to delivery to The University of Alberta Health Sciences Animal Center. An additional 3 to 4 days were required in the new environment before any experiment was conducted. All animals received a standard Purina monkey chow with additional fresh fruit twice weekly. All animals were found to be free from any sign of infection or communicable disease. None had any form of treatment for at least 14 days prior to the start of an experiment. Induction of subarachnoid hemorrhage was done in every experiment on each animal. Cerebral arteriography was done before and after each induction of subarachnoid hemorrhage. Each animal underwent three experiments at weekly intervals.

1. Operative Technique.

A. Anesthesia: A pre-anesthetic agent, pentobarbital sodium (Nembutal), 60 mg./kg. of body weight, was given intraperitoneally about 2 hours prior to induction of endotracheal anesthesia. Artificial ventilation was effected and respiratory rate maintained at 20 per minute using nitrous oxide and halothane, 0.75%; oxygen, 4 liters per minute; CO_2, 175 cc./minute and D-tubocurarine, 0.2 mg./kg., given intravenously.

B. Surgical preparation and position: Using a fine hair clipper fur was removed from the anterior portion of the cranium and lumbosacral areas. The subject was laid in supine position on the operating table, with limbs outstretched and secured.

Sterile surgical techniques were adhered to. Tincture of

ziphiran was used to prepare the operative sites and standard surgical drapes were applied. One and a half inch skin incisions were made on the left inguinal area on first experiments and on the right on second experiments. In the third experiments, either previous incision was reopened depending upon which side had the most suitable length of femoral artery.

Isolation of the femoral artery was done by taking into consideration its course and anatomic relations. It appears pinkish and lies dorsolateral to the somewhat bluish femoral vein underneath the femoral sheath. Excessive handling of the artery was avoided at all times to prevent vasospasm, which could prevent a successful catheterization. No hemostat forceps were applied to any segment of the femoral artery until catheterization was begun.

C. Catheterization of the femoral artery: A segment about 0.5 to 1 cm. distal to the takeoff of the profunda branch was the usual site of introduction, a method similar to that used by Ryan et al. [103]. A partially closed hemostat was applied just proximal to this site. A transverse incision was made in the anterior wall including half the circumference of the artery. No attempt to clamp the distal segment was made unless retrograde bleeding was excessive, since this stimulated the femoral artery into spasm. A siliconized no. 6 French catheter* 36 inches long was introduced via the femoral artery to the lower segment of the thoracic aorta. From there, exact placement of the tip of the catheter was guided fluoroscopically, up to that segment of the arch of the aorta where the brachiocephalic artery branches cranially. The use of guide wires was seldom necessary. Figure 1 shows antero-posterior

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* Racath, United States Catheter and Instrument Corp., Glens Falls, N.Y.

radiograph of a monkey demonstrating the major branches of the arch of the aorta.

A test dose of 1 to 2 cc. of radiographic contrast medium* (60% meglumine iothalamate) was injected to verify the precise location of the catheter tip. Symmetrical filling of both common carotid arteries was considered as the criterion for proper placement of the catheter, although filling only of the right side was preferred.

After termination of the experiment, the catheter was immediately withdrawn. Both segments of the femoral artery, proximal and distal to the arteriotomy were ligated with 4-0 black silk suture cut about .75 cm. from the last knot. This extra length of ligature facilitated location of the same artery on subsequent experiments.

During the entire procedure, the catheter was kept patent by occasional flushing with a few drops of physiologic saline solution with aqueous heparin sodium,† 1 unit/cc.

2. Radiographic Technique.

With the catheter tip in the brachiocephalic trunk, the animal was positioned to facilitate proper radiography. The head was supported with a nonopaque sponge which elevated it about an inch from the surface of the table. A well padded head holder set with an arm attachment to the side of the table was used to maintain position and to stabilize the endotracheal tubing without any manual assistance. This facilitated proper radiographic exposure of the entire cranium and at the same time prevented undue exposure of the investigators to radiation. Figure 2 shows the entire experimental setup.

---

* Conray, Mallinckrodt Pharmaceuticals, St. Louis, Mo.

† Riker Pharmaceutical Co. Ltd., Cooksville, Ontario.

FIGURE 1

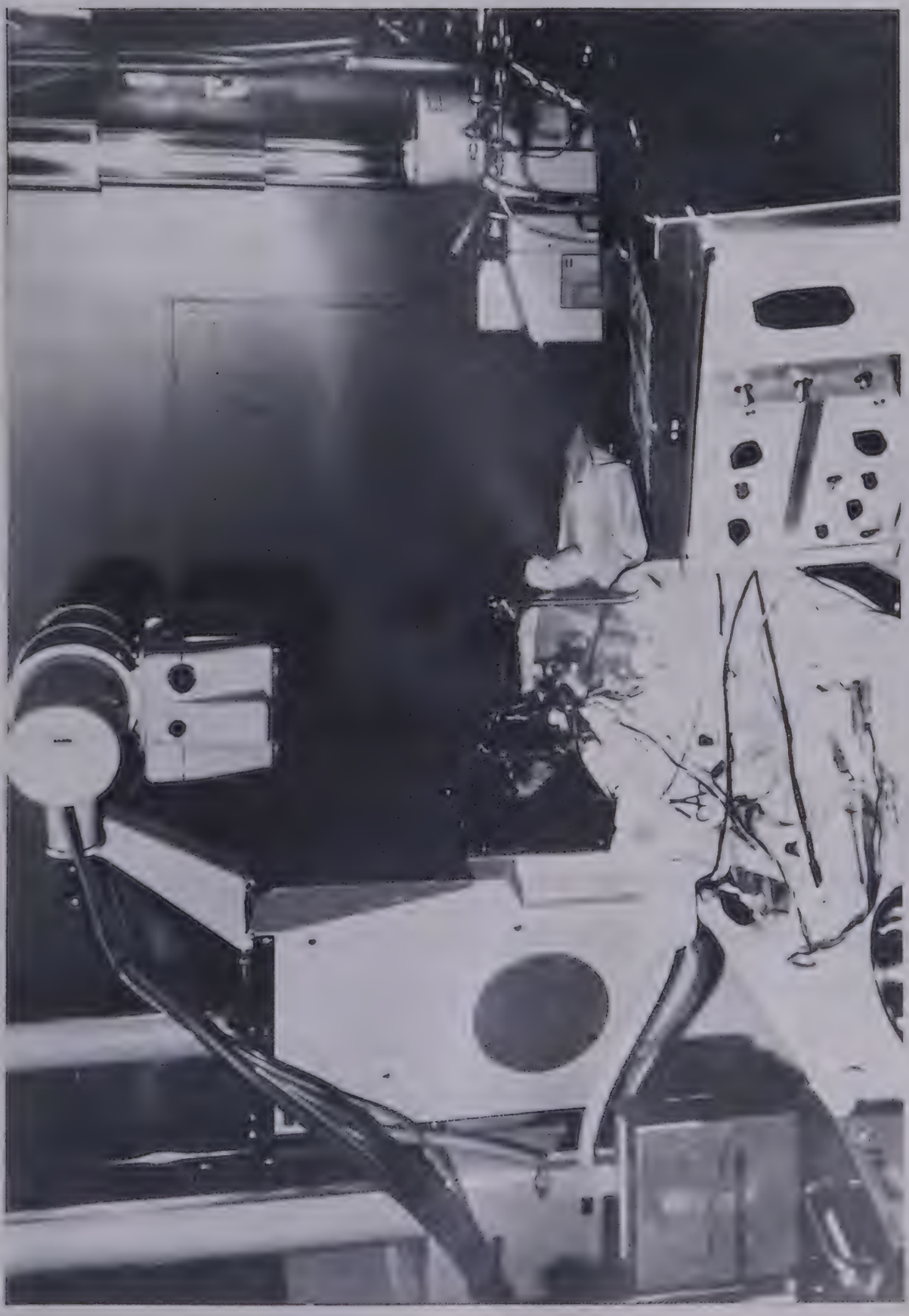

FIGURE 2

An antero-posterior and lateral serial film radiography was carried out using a 0.6 mm. focal spot with the Elema-Shonander biplane changer. Film exposure was 4/sec. for 1.5 second; 2/sec. for 2 seconds and 1/sec. for 2 seconds. Kodak royal blue films were used and processed in the 3.5 minute M4 Kodak processor. Exposure factors for the lateral projection were 100 milliamperes, 1/60 second at 87 KVP, and for the antero-posterior projection 100 milliamperes, 1/60 second at 77 KVP. Magnification was kept constant at 1.3:1 for midline structures in both projections.

For every cerebral arteriography, 8 cc. of 60% meglumine iothalamate was injected into the femoral catheter using a Cordis pressure injector at 400 psi. At most, 20 cc. of radiographic contrast medium was used in each experiment. Cerebral ateriography was done approximately 15 minutes before and 5 minutes after the induction of subarachnoid hemorrhage. Each of the 6 animals underwent 3 experiments at weekly intervals.

3. Induction of Subarachnoid Hemorrhage.

A twist drill hole was made in the midline of the cranium, 0.5 cm. from the nasion. This was performed prior to femoral catheterization. This same twist drill hole was subsequently used for the same purpose in the succeeding weekly experiments.

A 20G x 3" thin walled, short bevelled needle was introduced through the twist drill hole into the subarachnoid space overlying the midline of the planum phenoidale. The needle was directed in such a way that it passed between the tips of the frontal poles as it went inferiorly and posteriorly.

Accurate placement of the tip of the needle was guided radiographically. The needle was considered properly placed if it lay about

0.5 cm. anterior to the tuberculum sella. This final site of the tip of the needle was arbitrarily accepted to be anatomically in the area from which injected blood could easily circulate in the subarachnoid space and come into contact with the blood vessels to be observed.

Four cc. of fresh autogenous arterial blood was withdrawn from the femoral artery. To insure that the blood was not diluted, the catheter was allowed to drip slowly, until the physiologic saline solution used to keep it open was washed out completely. Induction of subarachnoid hemorrhage was accomplished by introduction of the blood sample through the needle originally inserted through the twist drill hole. Blood injection was done in 20 seconds, and the needle immediately withdrawn. Figure 3 shows a lateral radiograph of the monkey's head with the needle in proper position.

4. Measurements.

A Research Recorder Model PR-7, Electronics of Medicine, White Plains, N.Y. was used for measuring the experimental variables.

A. Systolic and diastolic blood pressure: This was recorded continuously by attaching a Statham pressure transducer, Model P23 Db to the proximal end of the femoral catheter. This system was calibrated so that a 1 mm. rise in the blood pressure trace from the base line represented 2 mm. of Hg.

B. Cerebrospinal fluid pressure: Lumbar punture was done usually at L_5-S_1 level with the premedicated animal supported in a sitting position. An 18G x 2.5 thin walled needle with a teflon catheter* was used for this purpose. Similarly, a Statham transducer was attached

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* Longdwel Catheter (Teflon), Becton, Dickinson and Company, Rutherford, N.J.

FIGURE 3

to this catheter for continuous recording. This input system was calibrated so that 1 mm. rise of CSF pressure represented 1 mm. of Hg.

C. Electrocardiographic recording: Tracings were done by attaching 3 standard unipolar limb leads and 3 unipolar precordial leads, according to the techniques described by Atta et al. [3].

Permanent photographic recordings of these three variables were taken at the start of every experiment; before and after each cerebral arteriogram; before and after the induction of subarachnoid hemorrhage; and at any time during the procedure when obvious changes were observed in the oscilloscope of the research recorder.

D. pCO_2, pH and pO_2 determinations: Blood samples for these measurements were taken before every cerebral arteriogram. The same technique was observed as in obtaining blood for induction of subarachnoid hemorrhage. A blood gas analyzer, Radiometer AME-1* was routinely used.

E. Temperature: Esophageal temperature was recorded, using a Yellow Spring's thermometer, in degrees Centrigrade. Frequency and sequence of measurements were the same as in (D).

F. Measurement of diameters of the supraclinoid segment of the internal carotid and the proximal segment of the pericallosal arteries: These were made using a micrometer applied directly on the radiographic films viewed in the X-ray box. All measurements were taken at the middle of the arterial phase as shown in the serial film radiographs. Measurements were done only of right lateral views. The antero-posterior views served to confirm the findings on the former and prevent radiographic misinterpretation.

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* Astrup Micro Equipment, Radiometer, Copenhagen.

Inasmuch as there are two supraclinoid segments, that of the left and right internal carotid arteries, only the right side was used for our purpose. The measurement of the diameter of the proximal pericallosal artery was simplified in view of the fact that rhesus monkeys have only one pericallosal trunk.

Comparable points for measurements on these two arteries were arbitrarily set up: for the supraclinoid segment of the internal carotid artery, measurements were done about 2 to 3 mm. superior to its commencement, while for the proximal segment of the pericallosal artery, 2 to 3 mm. from the point of union of the left and right anterior cerebral arteries. The same position on the artery was used in successive weeks.

All measurements using the micrometer were scaled to one hundredth of an inch. Referral to the measurements of these arteries in this particular unit has been avoided since we were concerned with relative and not absolute sizes.

CHAPTER V

STATISTICAL METHODS

STATISTICAL METHODS

Evaluation of the control and observed data were carried out using the following statistical methods:

A. Analysis of variance [110,118,125,126]: The ratio between the square of the differences of means of the control and observed data to the square of the means of the observed data represents the F statistic. By relating the F statistic in the F distribution chart, the P value is obtained. The P value represents the probability that the difference between the control and observed data occurred by chance.

Variance analysis is described by the F statistic where:

$$F = \frac{\text{MS between groups}}{\text{MS within groups}}$$ and

MS = mean square deviation

Results of the various analyses using the above method are presented in a manner similar to that outlined below.

Analysis of arterial diameter before subarachnoid hemorrhage over three weeks:

ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	SS	MS	F	P
TOT	17	12.500			
GRP	2	1.000	0.500	0.652	0.535
WTH	15	11.500	0.766		

Where:

TOT = total
GRP = between groups
WTH = within groups
DF = degree of freedom
SS = sum of squares
MS = mean square
F = F statistic
P = probability

Using a 0.05-level test, F will be: F .95 (2, 15) = 3.68. The observed F statistic (0.652) does not exceed the critical value of a 0.05-level test. Therefore, the hypothesis that *the diameter of the arteries before subarachnoid hemorrhage over the three weeks are not significantly different* is acceptable.

B. Student's t-test [110,118,125,126]: The ratio between the mean of the differences between paired samples to the standard error of the mean of the differences represents the Student's factor. By relating the Student's factor in the Student's distribution chart, the P value is obtained. This represents the probability that the difference in the paired samples occurred by chance. The following is the formula for the Student's t-test used in this study:

$$S = \sqrt{\frac{(d - \bar{d})^2}{n - 1}}$$

$$S\bar{d} = \frac{S}{n}$$

$$t = \frac{\bar{d}}{S\bar{d}}$$

Where:

S = standard deviation of the mean of the differences of paired samples

d = difference between paired samples

$\bar{d}$ = mean of the differences between paired samples

$S\bar{d}$ = standard error of the mean of the differences of paired samples

n = number of samples

t = Student factor

The results of the various statistical analyses using this method will be presented in a manner similar to that outlined below:

Analysis of CSF pressures before and after cerebral arteriogram:

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
9.67	10.00	2.87	2.65	10	-0.191	0.426

Where:

XBAR1 = mean of control samples

XBAR2 = mean of observed samples

SDEV1 = standard deviation of control samples

SDEV2 = standard deviation of observed samples

T = Student factor

P-one tail = probability

Using a 0.05-level test, the obtained P value indicated the hypothesis that *CSF pressures before and after cerebral arteriogram are not significantly different* is acceptable.

The level of significance was arbitrarily set at $\alpha = 0.05$ for all analyses in this study. All calculations were made using the IBM 360-67 computer. A schematic representation of the statistical approaches to the accumulated data is shown in Figure 4, analyses of blood vessel diameters; Figure 5, analyses of the effects of experimental variables on arterial response to induced SAH; Figure 6, analyses of blood pressures and heart rates.

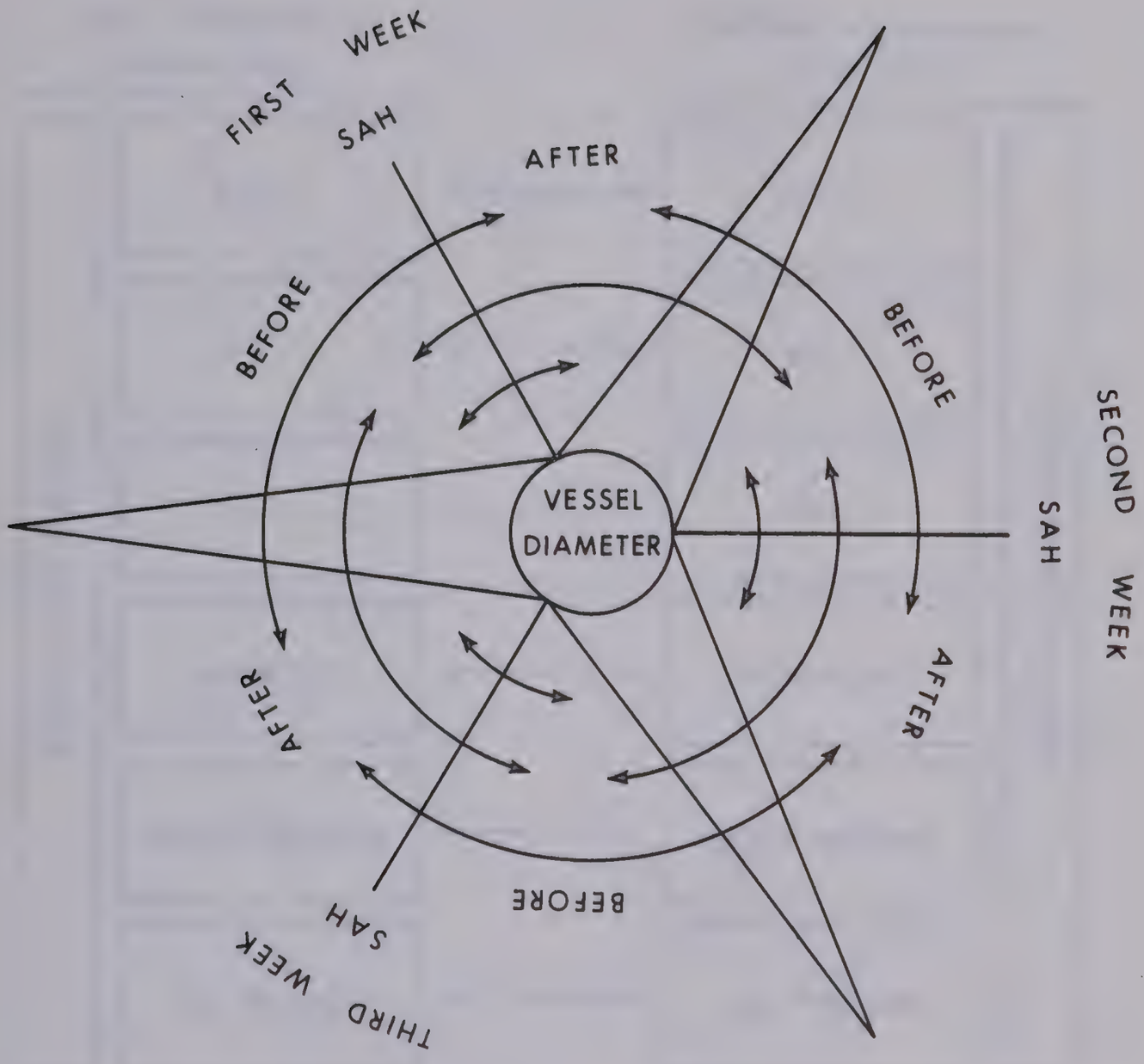


FIGURE 4 Schematic represenation of analyses of blood vessel diameters.

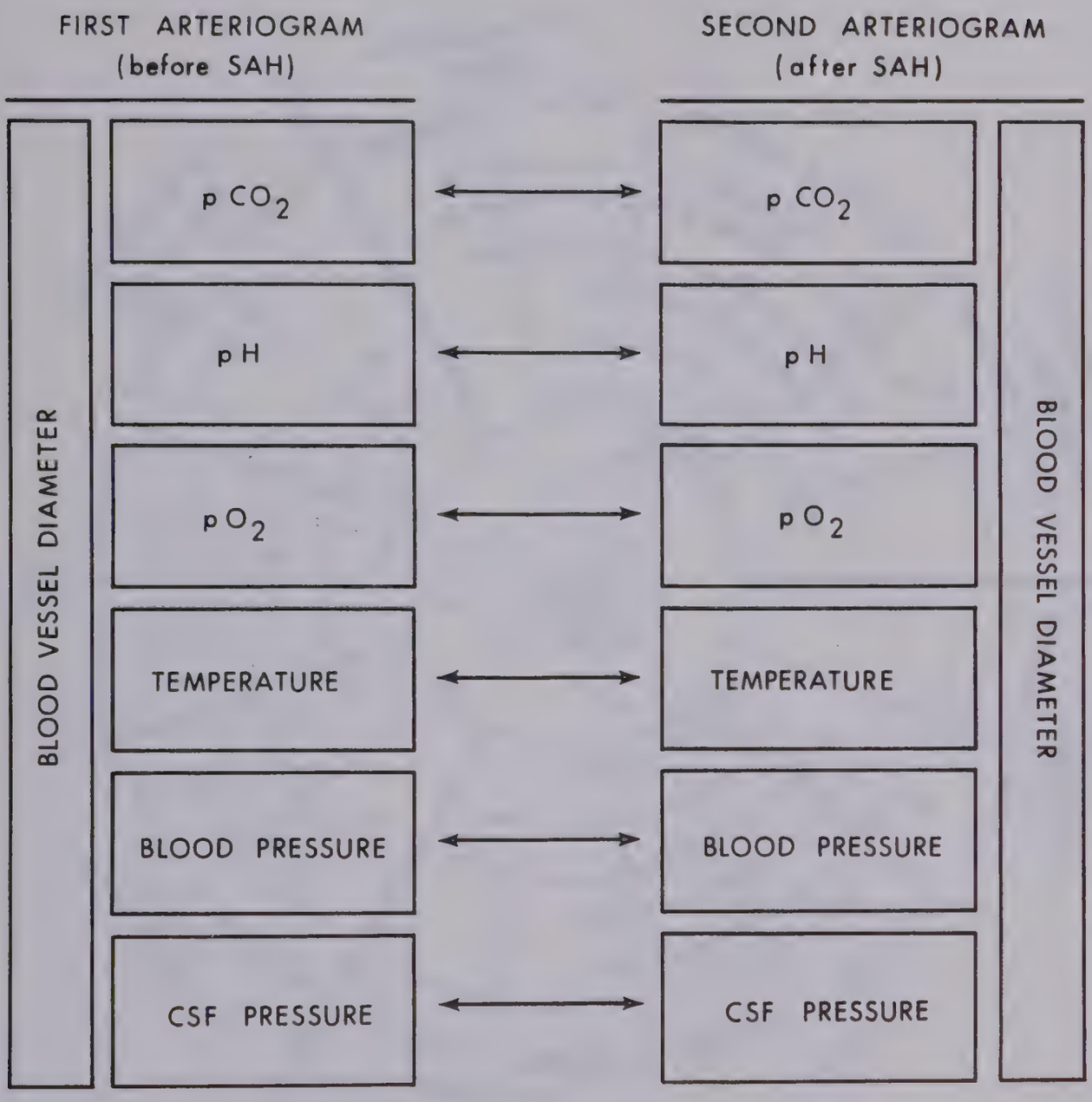


FIGURE 5 Schematic representation of analyses of the effects of experimental variables on arterial responses to induced SAH.

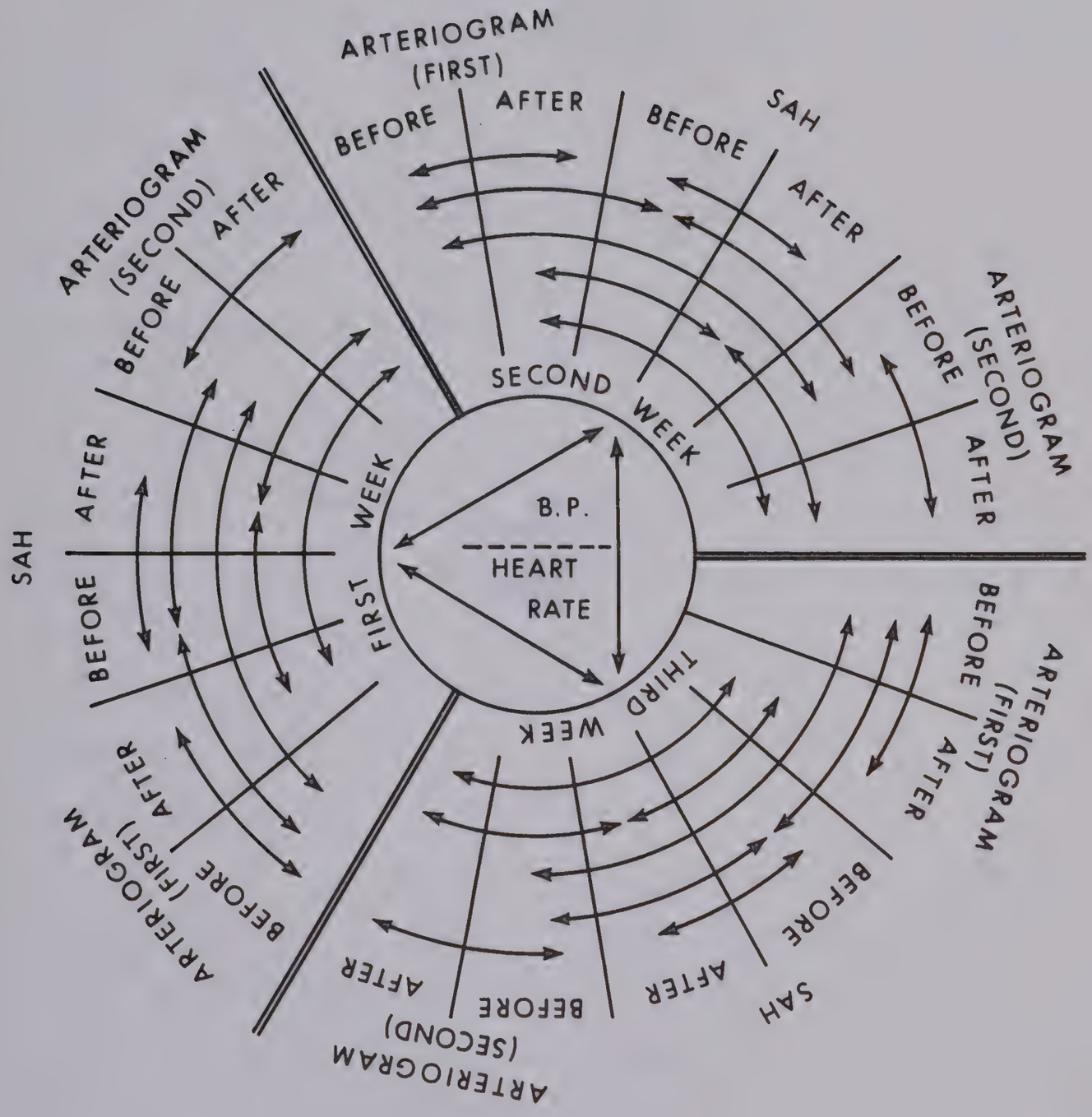


FIGURE 6 Schematic representation of analyses of mean blood pressures and heart rates.

RESULTS

1. Analyses of Blood Vessel Diameters.

A. Analyses of blood vessel diameters before and after induction of SAH:

Week I

Supraclinoid segment of right internal carotid artery.

ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	SS	MS	F	P
TOT	11	46.916			
GRP	1	14.083	14.083	4.289	0.065
WTH	10	32.833	3.283		

Comment: There was no significant difference in the diameter of this blood vessel before and after induction of SAH.

Proximal segment of pericallosal artery.

ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	SS	MS	F	P
TOT	11	52.250			
GRP	1	6.750	6.750	1.483	0.251
WTH	10	45.500	4.549		

Comment: There was no significant difference in the diameter of this blood vessel before and after induction of SAH.

Week II

Supraclinoid segment of right internal carotid artery.

ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	SS	MS	F	P
TOT	11	32.916			

GRP	1	24.083	24.083	27.263	0.000
WTH	10	8.833	0.883		

Comment: There was a significant difference in the diameter of this blood vessel before and after induction of SAH.

Proximal segment of pericallosal artery.

ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	SS	MS	F	P
TOT	11	42.916			
GRP	1	24.083	24.083	12.787	0.005
WTH	10	18.833	1.883		

Comment: There was a significant difference in the diameter of this blood vessel before and after induction of SAH.

Week III

Supraclinoid segment of right pericallosal artery.

ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	SS	MS	F	P
TOT	11	46.916			
GRP	1	14.083	14.083	4.289	0.065
WTH	10	32.833	3.283		

Comment: There was no significant difference in the diameter of this blood vessel before and after the induction of SAH.

Proximal segment of pericallosal artery.

ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	SS	MS	F	P
TOT	11	68.250			
GRP	1	24.083	24.083	5.452	0.042
WTH	10	44.166	4.416		

Comment: There was a significant difference in the diameter of this

blood vessel before and after the induction of SAH.

Figure 7 shows graphs of the six animals indicating the degree of spasm of the two observed arteries in three weeks of experimentation.

B. Analyses of blood vessel diameters before SAH over three weeks:

Supraclinoid segment of right pericallosal artery.

ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	SS	MS	F	P
TOT	17	12.500			
GRP	2	1.000	0.500	0.652	0.535
WTH	15	11.500	0.766		

Comment: There was no significant difference in the diameter of this blood vessel over three weeks before induction of SAH.

Proximal segment of pericallosal artery.

ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	SS	MS	F	P
TOT	17	27.777			
GRP	2	1.444	0.722	0.411	0.670
WTH	15	26.333	1.755		

Comment: There was no significant difference in the diameter of this blood vessel over three weeks before induction of SAH.

C. Analyses of blood vessel diameters after SAH over three weeks:

Supraclinoid segment of right internal carotid artery.

ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	SS	MS	F	P
TOT	17	63.111			
GRP	2	0.110	5.541	1.319	0.987
WTH	15	63.000	4.200		

Comment: There was no significant difference in the diameter of this

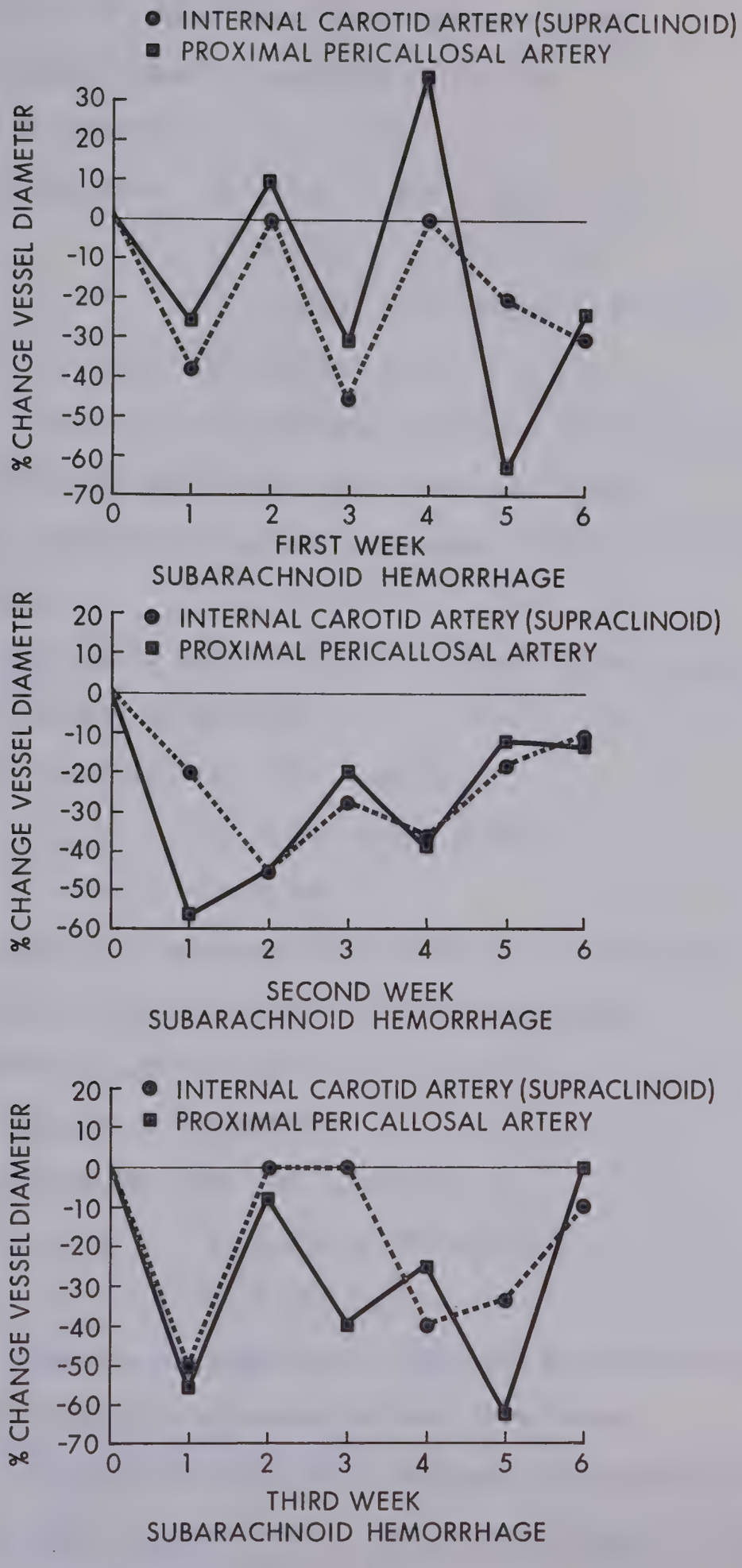

INTERNAL CAROTID ARTERY (SUPRACLINOID)
PROXIMAL PERICALLOSAL ARTERY
% CHANGE VESSEL DIAMETER
30
20
10
0
-10
-20
-30
-40
-50
-60
-70
0 1 2 3 4 5 6
FIRST WEEK
SUBARACHNOID HEMORRHAGE
INTERNAL CAROTID ARTERY (SUPRACLINOID)
PROXIMAL PERICALLOSAL ARTERY
% CHANGE VESSEL DIAMETER
20
10
0
-10
-20
-30
-40
-50
-60
0 1 2 3 4 5 6
SECOND WEEK
SUBARACHNOID HEMORRHAGE
INTERNAL CAROTID ARTERY (SUPRACLINOID)
PROXIMAL PERICALLOSAL ARTERY
% CHANGE VESSEL DIAMETER
20
10
0
-10
-20
-30
-40
-50
-60
-70
0 1 2 3 4 5 6
THIRD WEEK
SUBARACHNOID HEMORRHAGE

FIGURE 7

blood vessel over three weeks after induction of SAH.

Proximal segment of pericallosal artery.

ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	SS	MS	F	P
TOT	17	84.500			
GRP	2	2.333	1.166	0.212	0.811
WTH	15	82.166	5.477		

Comment: There was no significant difference in the diameter of this blood vessel over three weeks after induction of SAH.

D. Analyses of degrees of response of blood vessels to SAH over three weeks:

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	MS	ADJ F	P
GRP	2	0.765	0.204	0.818
WTH	14	3.748		

Comment: There was no significant difference in the degree of response of this blood vessel to induced SAH over three weeks.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	MS	ADJ F	p
GRP	2	2.484	0.494	0.620
WTH	14	5.022		

Comment: There was no significant difference in the degree of response of this blood vessel to induced SAH over three weeks.

E. Analysis of difference of degrees of response of supraclinoid segment of right internal carotid and proximal segment of pericallosal arteries to induced SAH:

Week I

ADJUSTED ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	MS	ADJ F	P
GRP	1	0.170	3.003	0.866
WTH	9	5.686		

Comment: There was no significant difference in the degree of response to induced SAH between the two arteries.

Week II

ADJUSTED ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	MS	ADJ F	P
GRP	1	9.100	3.189	0.862
WTH	9	2.852		

Comment: There was no significant difference in the degree of response to induced SAH between the two arteries.

Week III

ADJUSTED ANALYSIS OF VARIANCE

SOURCE OF VARIATION	DF	MS	ADJ F	P
GRP	1	6.713	1.496	0.991
WTH	9	4.486		

Comment: There was no significant difference in the degree of response to induced SAH between the two arteries.

Figures 8 and 9 show lateral arteriograms taken before and after induction of SAH respectively. Figures 10 and 11 show antero-posterior arteriograms taken before and after induction of SAH respectively.

2. Analysis of experimental variables.

A. pCO_2:

i. Analyses of pCO_2 values during first and second arteriograms.

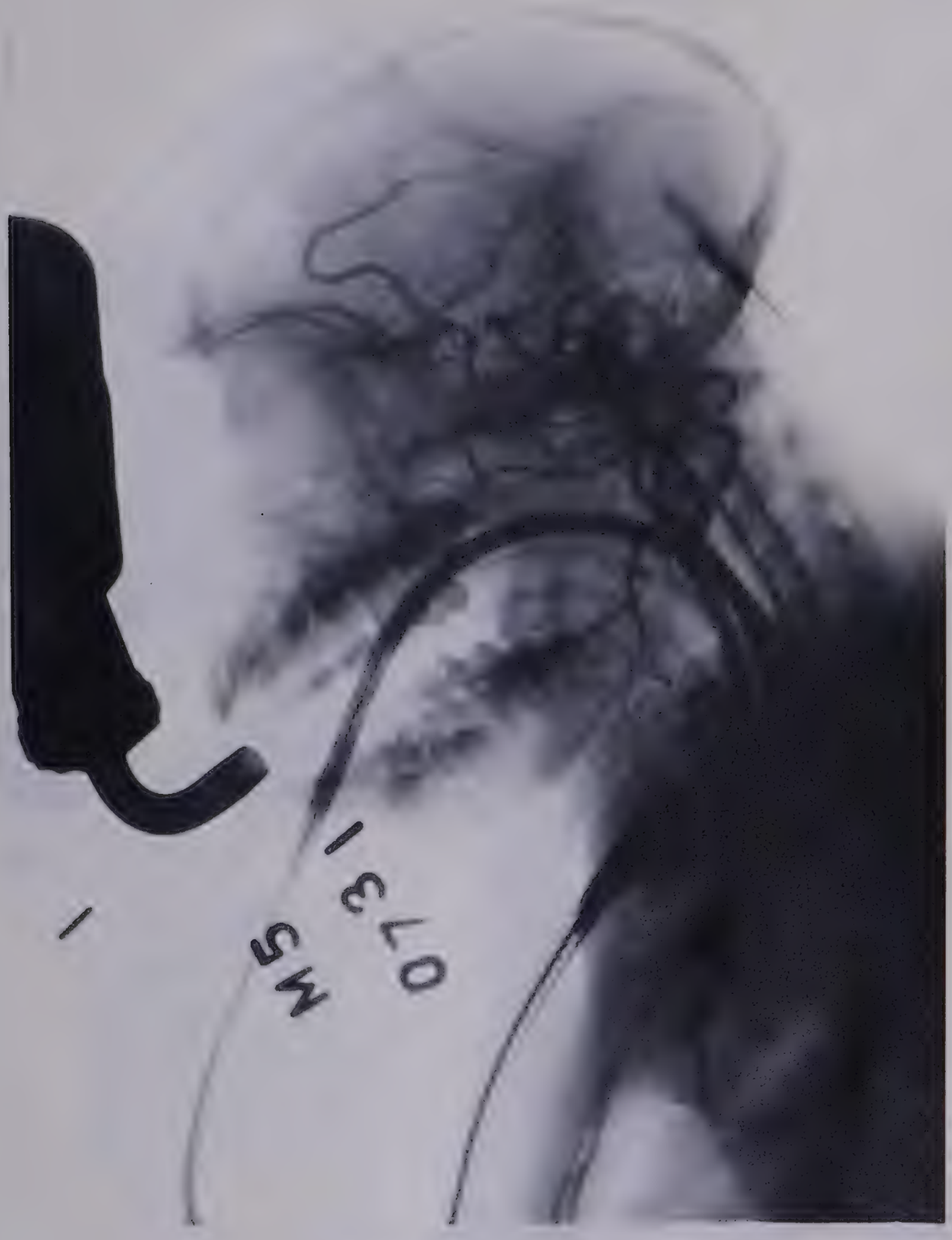


FIGURE 8

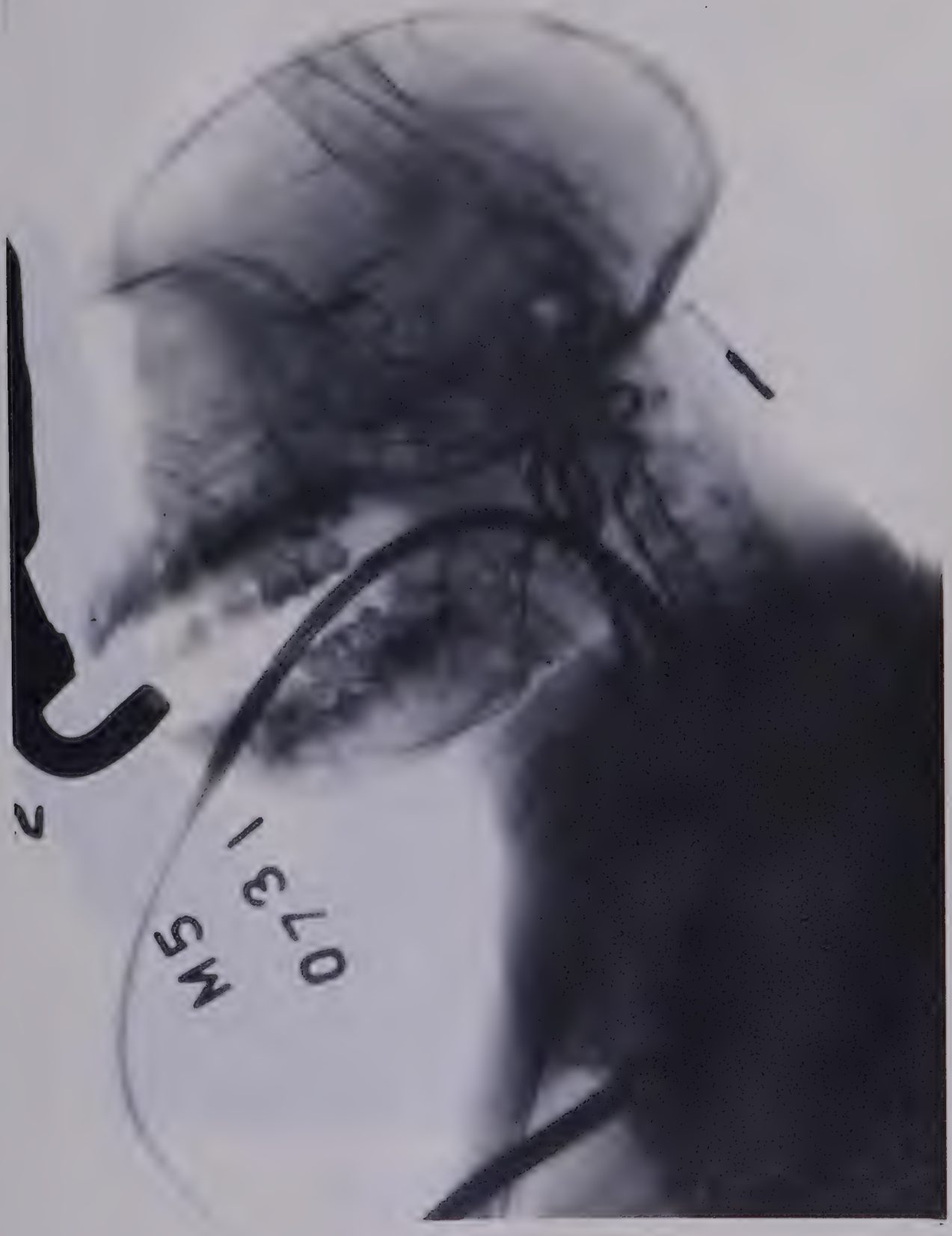


FIGURE 9

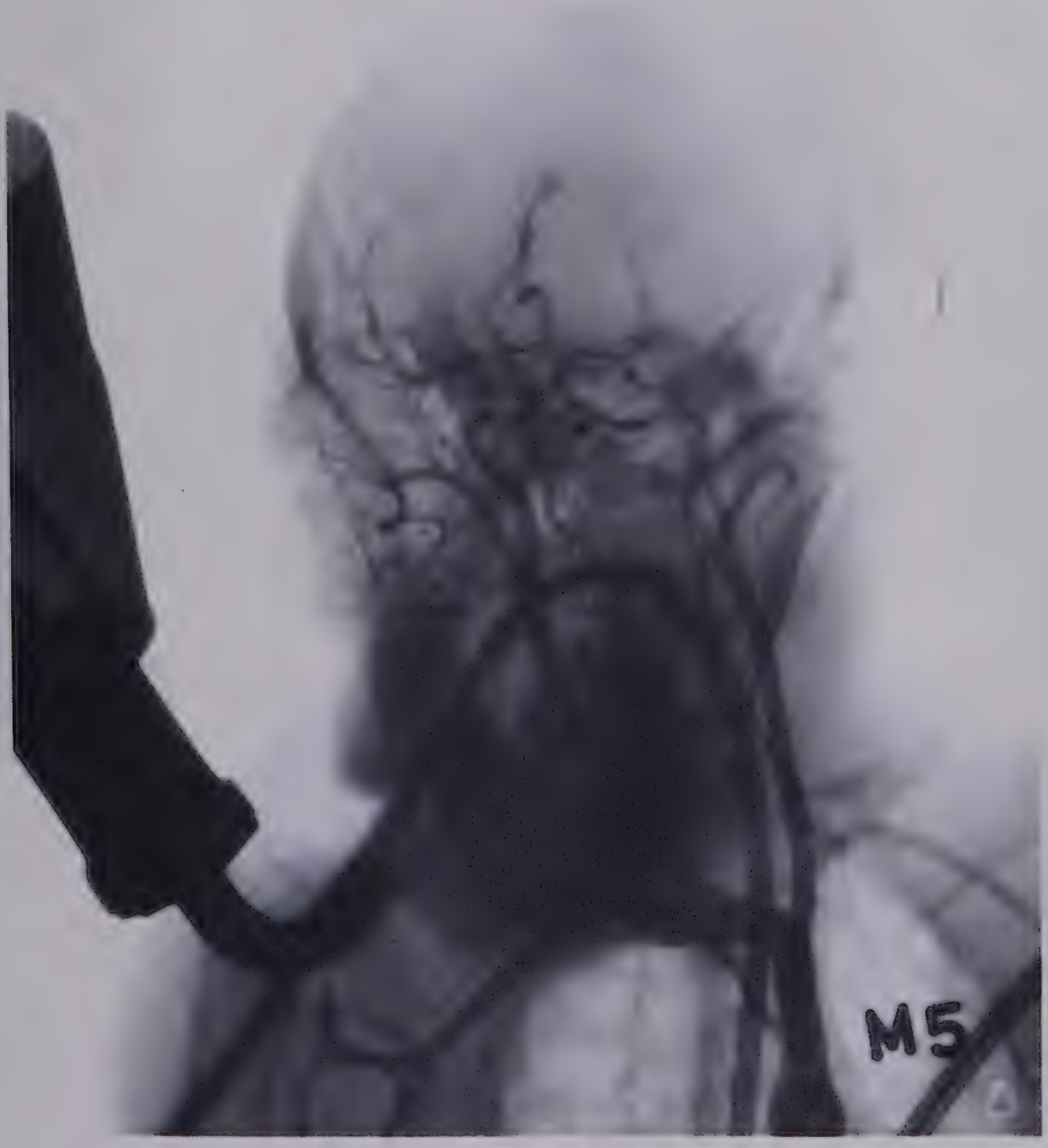


FIGURE 10

FIGURE 11

ANALYSIS OF VARIANCE

Week I F = 1.745 P = 0.216

Comment: There was no significant difference of pCO_2 values during the first and second arteriograms.

Week II F = 2.542 P = 0.876

Comment: There was no significant difference of pCO_2 values during the first and second arteriograms.

Week III F = 0.597 P = 0.457

Comment: There was no significant difference of pCO_2 values during the first and second arteriograms.

ii. Analysis of pCO_2 values at first arteriograms over three weeks.

ANALYSIS OF VARIANCE F = 0.680 P = 0.519

Comment: There was no significant difference of pCO_2 values at the time of first arteriograms over three weeks.

iii. Analysis of pCO_2 values at second arteriograms over three weeks.

ANALYSIS OF VARIANCE F = 0.630 P = 0.547

Comment: There was no significant difference of pCO_2 values at the time of second arteriograms over three weeks.

iv. Analyses of degrees of change of vessel diameters with pCO_2 as control.

Week I

Control: mean pCO_2 = 51.416 mm. Hg

Observed: mean pCO_2 = 47.333 mm. Hg

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 4.289 P = 0.065 (pCO_2 effect not considered)

ADJUSTED F = 4.588 P = 0.061 (pCO_2 as control)

Comment: The pCO_2 effect on the diameter of this blood vessel was towards vasoconstriction.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 1.483 P = 0.251 (pCO_2 effect not considered)

ADJUSTED F = 0.999 P = 0.344 (pCO_2 as control)

Comment: The pCO_2 effect on the diameter of this blood vessel was towards vasodilation.

Week II

Control: mean pCO_2 = 45.916 mm. Hg

Observed: mean pCO_2 = 46.583 mm. Hg

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 27.263 P = 0.000 (pCO_2 effect not considered)

ADJUSTED F = 24.484 P = 0.001 (pCO_2 as control)

Comment: The pCO_2 effect on the diameter of this blood vessel was towards vasodilation.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 12.787 P = 0.005 (pCO_2 effect not considered)

ADJUSTED F = 11.698 P = 0.008 (pCO_2 as control)

Comment: The pCO_2 effect on the diameter of this blood vessel was towards vasodilation.

Week III

Control: mean pCO_2 = 47.666 mm. Hg

Observed: mean pCO_2 = 44.083 mm. Hg

Supraclinoid segment of right pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 4.289 P = 0.065 (pCO_2 effect not considered)

ADJUSTED F = 4.588 P = 0.061 (pCO_2 as control)

Comment: The pCO_2 effect on the diameter of this blood vessel was towards vasoconstriction.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 5.452 P = 0.042 (pCO_2 effect not considered)

ADJUSTED F = 5.939 P = 0.038 (pCO_2 as control)

Comment: The pCO_2 effect on the diameter of this blood vessel was towards vasoconstriction.

B. pH:

i. Analyses of pH values during first and second arteriograms.

ANALYSIS OF VARIANCE

Week I F = 0.283 P = 0.606

Comment: There was no significant difference of pH values during the first and second arteriograms.

Week II F = 0.833 P = 0.383

Comment: There was no significant difference of pH values during the first and second arteriograms.

Week III F = 5.154 P = 1.000

Comment: There was no signficant difference of pH values during the first and second arteriograms.

ii. Analysis of pH values at first arteriograms over three weeks.

ANALYSIS OF VARIANCE F = 1.630 P = 0.229

Comment: There was no significant difference of pH values at the time of first arterigrams over three weeks.

iii. Analysis of pH values at second arteriograms over three weeks.

ANALYSIS OF VARIANCE F = 2.230 P = 0.142

Comment: There was no significant difference of pH values at the time of second arteriograms over three weeks.

iv. Analyses of degrees of change of vessel diameters with pH as control.

Week I

Control: mean pH = 7.351

Observed: mean pH = 7.334

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 4.289 P = 0.065 (pH effect not considered)

ADJUSTED F = 6.129 P = 0.035 (pH as control)

Comment: The pH effect on the diameter of this blood vessel was towards vasoconstriction.

Proximal segment of pericallosal artery.

UNADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 1.483 P = 0.251 (pH effect not considered)

ADJUSTED F = 1.201 P = 0.301 (pH as control)

Comment: The pH effect on the diameter of this blood vessel was towards vasodilation.

Week II

Control: mean pH = 7.381

Observed: mean pH = 7.358

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 27.263 P = 0.000 (pH effect not considered)

ADJUSTED F = 26.188 P = 0.001 (pH as control)

Comment: The pH effect on the diameter of this blood vessel was towards vasodilation.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 12.787 P = 0.005 (pH effect not considered)

ADJUSTED F = 10.617 P = 0.010 (pH as control)

Comment: The pH effect on the diameter of this blood vessel was towards vasodilation.

Week III

Control: mean pH = 7.413

Observed: mean pH = 7.406

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 4.289 P = 0.065 (pH effect not considered)

ADJUSTED F = 3.824 P = 0.082 (pH as control)

Comment: The pH effect on the diameter of this blood vessel was towards vasodilation.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 5.452 P = 0.042 (pH effect not considered)

ADJUSTED F = 4.899 P = 0.054 (pH as control)

Comment: The pH effect on the diameter of this blood vessel was towards vasodilation.

C. pO_2:

i. Analyses of pO_2 values during the first and second arteriograms.

ANALYSIS OF VARIANCE

Week I F = 2.392 P = 0.880

Comment: There was no significant difference of pO_2 values during the first and second arteriograms.

Week II F = 0.115 P = 0.741

Comment: There was no significant difference of pO_2 values during the first and second arteriograms.

Week III F = 0.834 P = 0.382

Comment: There was no significant difference of pO_2 values during the first and second arteriograms.

ii. Analysis of pO_2 values at first arteriograms over three weeks.

ANALYSIS OF VARIANCE F = 0.830 P = 0.455

Comment: There was no significant difference in the pO_2 values at the time of first arteriograms over three weeks.

iii. Analysis of pO_2 values at second arteriograms over three weeks.

ANALYSIS OF VARIANCE F = 2.300 P = 0.134

Comment: There was no significant difference of pO_2 values at the time of second arteriograms over three weeks.

iv. Analyses of degrees of change of vessel diameters with pO_2 as control.

Week I

Control: mean pO_2 = 298.500

Observed: mean pO_2 = 305.00

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 4.289 P = 0.065 (pO_2 effect not considered)

ADJUSTED F = 3.830 P = 0.082 (pO_2 as control)

Comment: The pO_2 effect on the diameter of this blood vessel was towards vasodilation.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 1.483 P = 0.251 (pO_2 effect not considered)

ADJUSTED F = 2.167 P = 0.175 (pO_2 as control)

Comment: The pO_2 effect on the diameter of this blood vessel was towards vasoconstriction.

Week II

Control: mean pO_2 = 339.166 mm. Hg

Observed: mean pO_2 = 345.833 mm. Hg

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 27.263 P = 0.000 (pO_2 effect not considered)

ADJUSTED F = 24.252 P = 0.001 (pO_2 as control)

Comment: The pO_2 effect on the diameter of this blood vessel was towards vasodilation.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 12.787 P = 0.005 (pO_2 effect not considered)

ADJUSTED F = 12.325 P = 0.007 (pO_2 as control)

Comment: The pO_2 effect on the diameter of this blood vessel was towards vasodilation.

Week III

Control: mean pO_2 = 334.333 mm. Hg

Observed: mean pO_2 = 356.666 mm. Hg

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 4.289 P = 0.065 (pO_2 effect not considered)

ADJUSTED F = 3.024 P = 0.116 (pO_2 as control)

Comment: The pO_2 effect on the diameter of this blood vessel was towards vasodilation.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 5.452 P = 0.042 (pO_2 effect not considered)

ADJUSTED F = 4.120 P = 0.073 (pO_2 as control)

Comment: The pO_2 effect on the diameter of this blood vessel was towards vasodilation.

D. Temperature:

i. Analyses of temperature readings during the first and second arteriograms.

ANALYSIS OF VARIANCE

Week I F = 1.597 P = 0.235

Comment: There was no significant difference of temperatures during the first and second arteriograms.

Week II F = 0.582 P = 0.463

Comment: There was no significant difference of temperatures during the first and second arteriograms.

Week III F = 0.127 P = 0.728

Comment: There was no significant difference of temperatures during the first and second arteriograms.

ii. Analysis of temperature readings at first arteriograms over three weeks.

ANALYSIS OF VARIANCE F = 1.000 P = 0.392

Comment: There was no significant difference of temperatures at the time of first arteriograms over three weeks.

iii. Analysis of temperature readings at second arteriograms over three weeks.

ANALYSIS OF VARIANCE F = 0.190 P = 0.832

Comment: There was no significant difference of temperatures at the time of second arteriograms over three weeks.

iv. Analysis of degrees of change of vessel diameters with

temperature as control.

Week I

Control: mean temperature = 34.541°C

Observed: mean temperature = 33.333°C

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 4.289 P = 0.065 (temperature effect not considered)

ADJUSTED F = 4.582 P = 0.061 (temperature as control)

Comment: The temperature effect on the diameter of this blood vessel was towards vasoconstriction.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 1.483 P = 0.251 (temperature effect not considered)

ADJUSTED F = 3.657 P = 0.088 (temperature as control)

Comment: The temperature effect on the diameter of this blood vessel was towards vasoconstriction.

Week II

Control: mean temperature = 33.349°C

Observed: mean temperature = 32.791°C

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 27.263 P = 0.000 (temperature effect not considered)

ADJUSTED F = 23.008 P = 0.001 (temperature as control)

Comment: The temperature effect on the diameter of this blood vessel was towards vasodilation.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 12.787 P = 0.005 (temperature effect not considered)

ADJUSTED F = 10.781 P = 0.009 (temperature as control)

Comment: The temperature effect on the diameter of this blood vessel was towards vasodilation.

Week III

Control: mean temperature = 33.433°C

Observed: mean temperature = 33.066°C

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 4.289 P = 0.065 (temperature effect not considered)

ADJUSTED F = 4.424 P = 0.065 (temperature as control)

Comment: The temperature change had no effect on the diameter of this blood vessel.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 5.452 P = 0.042 (temperature effect not considered)

ADJUSTED F = 5.344 P = 0.046 (temperature as control)

Comment: The temperature effect on the diameter of this blood vessel was towards vasodilation.

E. Blood pressure:

i. Analyses of mean blood pressures during the first and second arteriograms.

ANALYSIS OF VARIANCE

Week I F = 0.594 P = 0.459

Comment: There was no significant difference of mean blood pressures during the first and second arteriograms.

Week II F = 0.226 P = 0.645

Comment: There was no significant difference of mean blood pressures during the first and second arteriograms.

Week III F = 0.140 P = 0.715

Comment: There was no significant difference of mean blood pressures during the first and second arteriograms.

ii. Analysis of mean blood pressures at first arteriograms over three weeks.

ANALYSIS OF VARIANCE F = 0.340 P = 0.719

Comment: There was no significant difference in mean blood pressures at the time of first arteriograms over three weeks.

iii. Analysis of mean blood pressures at second arteriograms over three weeks.

ANALYSIS OF VARIANCE F = 0.120 P = 0.885

Comment: There was no significant difference in mean blood pressures at the time of second arteriograms over three weeks.

iv. Analyses of degrees of change of vessel diameters with blood pressure as control.

Week I

Control: mean blood pressure = 65.996 mm. Hg

Observed: mean blood pressure = 58.996 mm. Hg

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 4.289 P = 0.065 (blood pressure effect not considered)

ADJUSTED F = 3.539 P = 0.093 (blood pressure as control)

Comment: The blood pressure effect on the diameter of this blood vessel was towards vasodilation.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 1.483 P = 0.251 (blood pressure effect not considered)

ADJUSTED F = 2.239 P = 0.169 (blood pressure as control)

Comment: The blood pressure effect on the diameter of this blood vessel was towards vasoconstriction.

Week II

Control: mean blood pressure = 57.608 mm. Hg

Observed: mean blood pressure = 62.053 mm. Hg

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 27.263 P = 0.000 (blood pressure effect not considered)

ADJUSTED F = 31.918 P = 0.000 (blood pressure as control)

Comment: The blood pressure change had no effect on the diameter of this blood vessel.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 12.787 P = 0.005 (blood pressure effect not considered)

ADJUSTED F = 11.096 P = 0.009 (blood pressure as control)

Comment: The blood pressure effect on the diameter of this blood vessel was towards vasodilation.

Week III

Control: mean blood pressure = 61.661 mm. Hg

Observed: mean blood pressure = 57.884 mm. Hg

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 4.289 P = 0.065 (blood pressure effect not considered)

ADJUSTED F = 4.528 P = 0.062 (blood pressure as control)

Comment: The blood pressure effect on the diameter of this blood vessel was towards vasoconstriction.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 5.452 P = 0.042 (blood pressure effect not considered)

ADJUSTED F = 6.637 P = 0.030 (blood pressure as control)

Comment: The blood pressure effect on the diameter of this blood vessel was towards vasoconstriction.

F. CSF pressure:

i. Analyses of CSF pressures during the first and second arteriograms.

ANALYSIS OF VARIANCE

Week I F = 4.900 P = 0.051

Comment: There was a significant difference of CSF pressures during the first and second arteriograms.

Week II F = 5.680 P = 0.038

Comment: There was a significant difference of CSF pressures during the first and second arteriograms.

Week III F = 1.171 P = 0.219

Comment: There was no significant difference in CSF pressures during the first and second arteriograms.

ii. Analyses of degrees of change of vessel diameters with CSF pressure as control.

Week I

Control: mean CSF pressure = 9.666 mm. Hg

Observed: mean CSF pressure = 22.666 mm. Hg

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 4.289 P = 0.065 (CSF pressure effect not considered)

ADJUSTED F = 11.509 P = 0.008 (CSF pressure as control)

Comment: The CSF pressure effect on the diameter of this blood vessel was towards vasoconstriction.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 1.483 P = 0.251 (CSF pressure effect not considered)

ADJUSTED F = 2.813 P = 0.128 (CSF pressure as control)

Comment: The CSF pressure effect on the diameter of this blood vessel was towards vasoconstriction.

Week II

Control: mean CSF pressure = 10.000 mm. Hg

Observed: mean CSF pressure = 39.166 mm. Hg

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 27.263 P = 0.000 (CSF pressure effect not considered)

ADJUSTED F = 17.906 P = 0.002 (CSF pressure as control)

Comment: The CSF pressure effect on the diameter of this blood vessel was towards vasodilation.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 12.787 P = 0.005 (CSF pressure effect not considered)

ADJUSTED F = 6.277 P = 0.034 (CSF pressure as control)

Comment: The CSF pressure effect on the diameter of this blood vessel was towards vasodilation.

Week III

Control: mean CSF pressure = 12.166 mm. Hg

Observed: mean CSF pressure = 29.833 mm. Hg

Supraclinoid segment of right internal carotid artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 4.289 P = 0.065 (CSF pressure effect not considered)

ADJUSTED F = 2.148 P = 0.177 (CSF pressure as control)

Comment: The CSF pressure effect on the diameter of this blood vessel was towards vasodilation.

Proximal segment of pericallosal artery.

ADJUSTED ANALYSIS OF VARIANCE

UNADJUSTED F = 5.452 P = 0.042 (CSF pressure effect not considered)

ADJUSTED F = 3.633 P = 0.089 (CSF pressure as control)

Comment: The CSF pressure effect on the diameter of this blood vessel was towards vasodilation.

3. Related Observations.

Blood Pressure:

Blood pressure recordings were made consecutively before and after the first arteriogram, the induction of SAH and the second arteriogram.

A. Analyses of mean blood pressures before and after the first arteriograms.

Week I (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
66.00	52.27	13.30	10.07	10	1.839	0.047

Comment: There was a significant difference of mean blood pressures before and after first arteriograms.

Week II (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
57.66	33.77	17.75	6.91	10	2.797	0.009

Comment: There was a significant difference of mean blood pressures before and after first arteriograms.

Week III (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
61.66	43.49	17.11	13.06	10	1.887	0.044

Comment: There was a significant difference of mean blood pressures before and after first arteriograms.

Figure 12 shows a cumulative frequency graph of the six animals indicating the blood pressure changes after the first arteriogram in three weeks of experimentation.

B. Analyses of mean blood pressures before and after induction of SAH.

Week I (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
58.00	66.11	6.89	13.96	10	-1.165	0.135

Comment: There was no significant difference of mean blood pressures before and after induction of SAH.

Week II (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
44.88	74.32	14.06	12.78	10	-3.465	0.003

Comment: There was a significant difference of mean blood pressures before and after induction of SAH.

Week III (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
53,33	63.44	13.30	12.81	10	-0.982	0.174

Comment: There was no significant difference of mean blood pressures before and after induction of SAH.

Figure 13 shows a cumulative frequency graph of the six animals indicating the blood pressure changes after induction of SAH in three weeks of experimentation.

C. Analyses of mean blood pressures before and after second arteriogram.

Week I (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
59.00	46.77	15.34	17.72	10	1.166	0.135

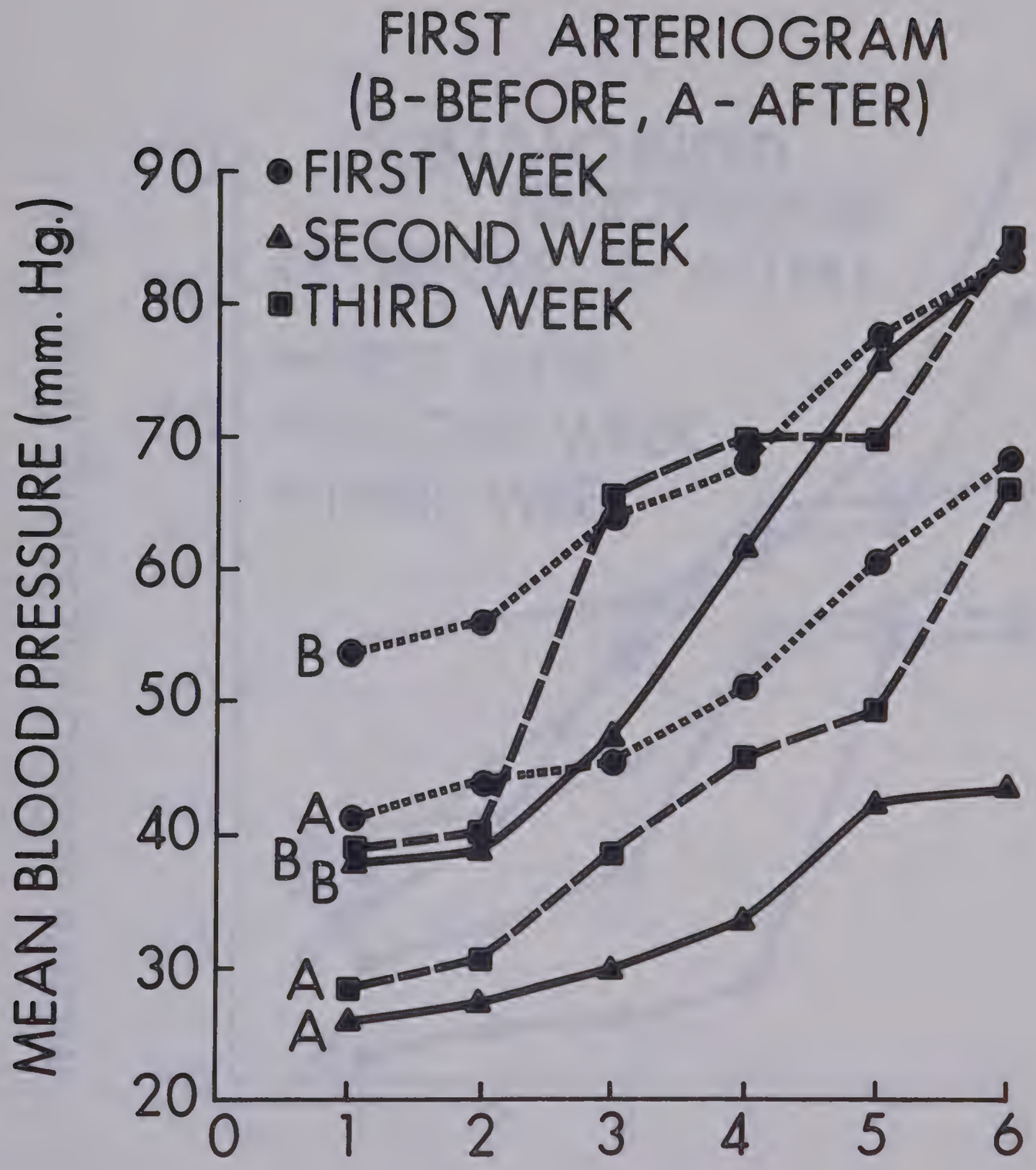
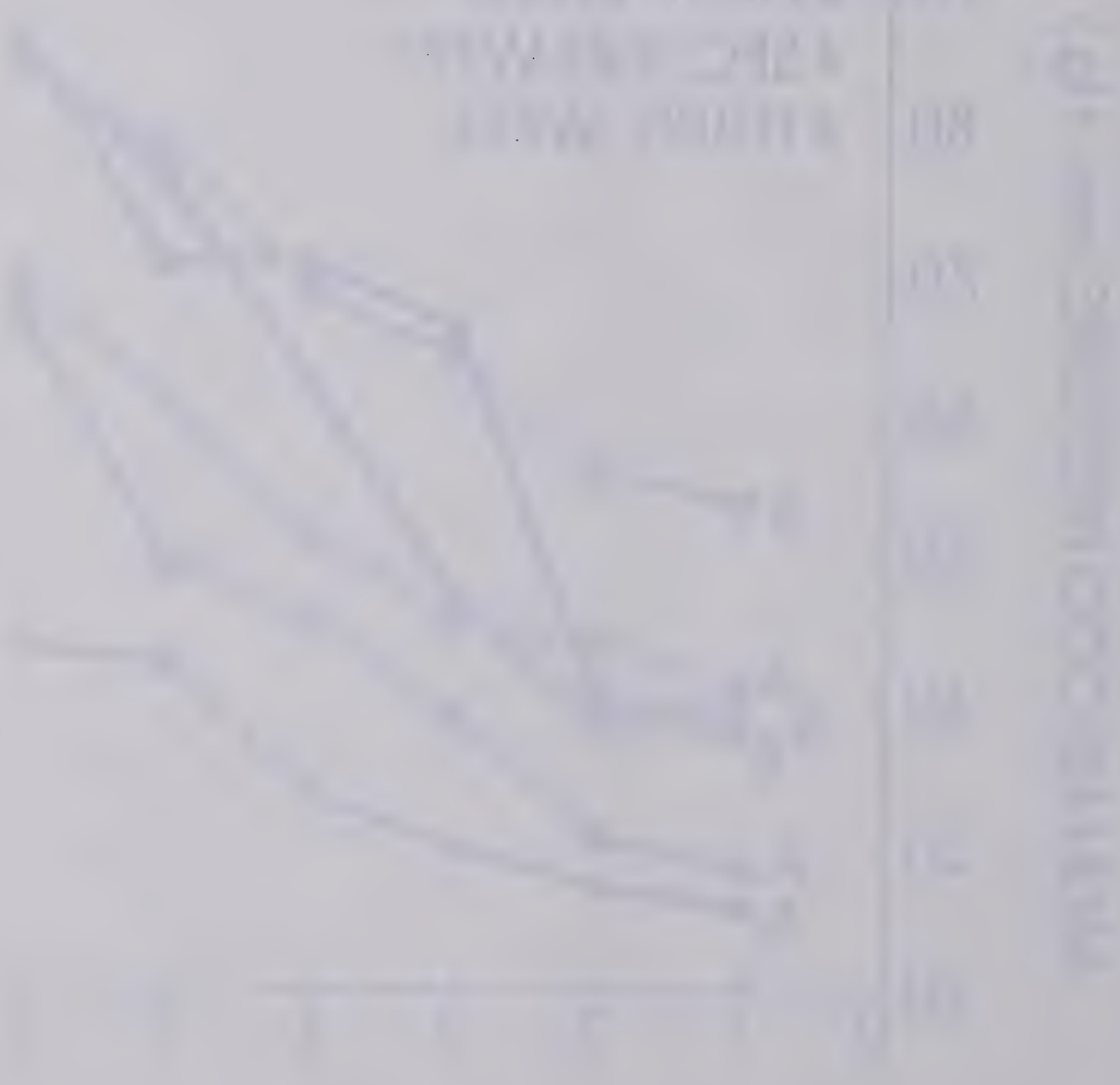

FIRST ARTERIOGRAM
(B-BEFORE, A-AFTER)
FIRST WEEK
SECOND WEEK
THIRD WEEK
MEAN BLOOD PRESSURE (mm. Hg.)
90
80
70
60
50
40
30
20
0
1
2
3
4
5
6
B
A
B
B
A
A

FIGURE 12



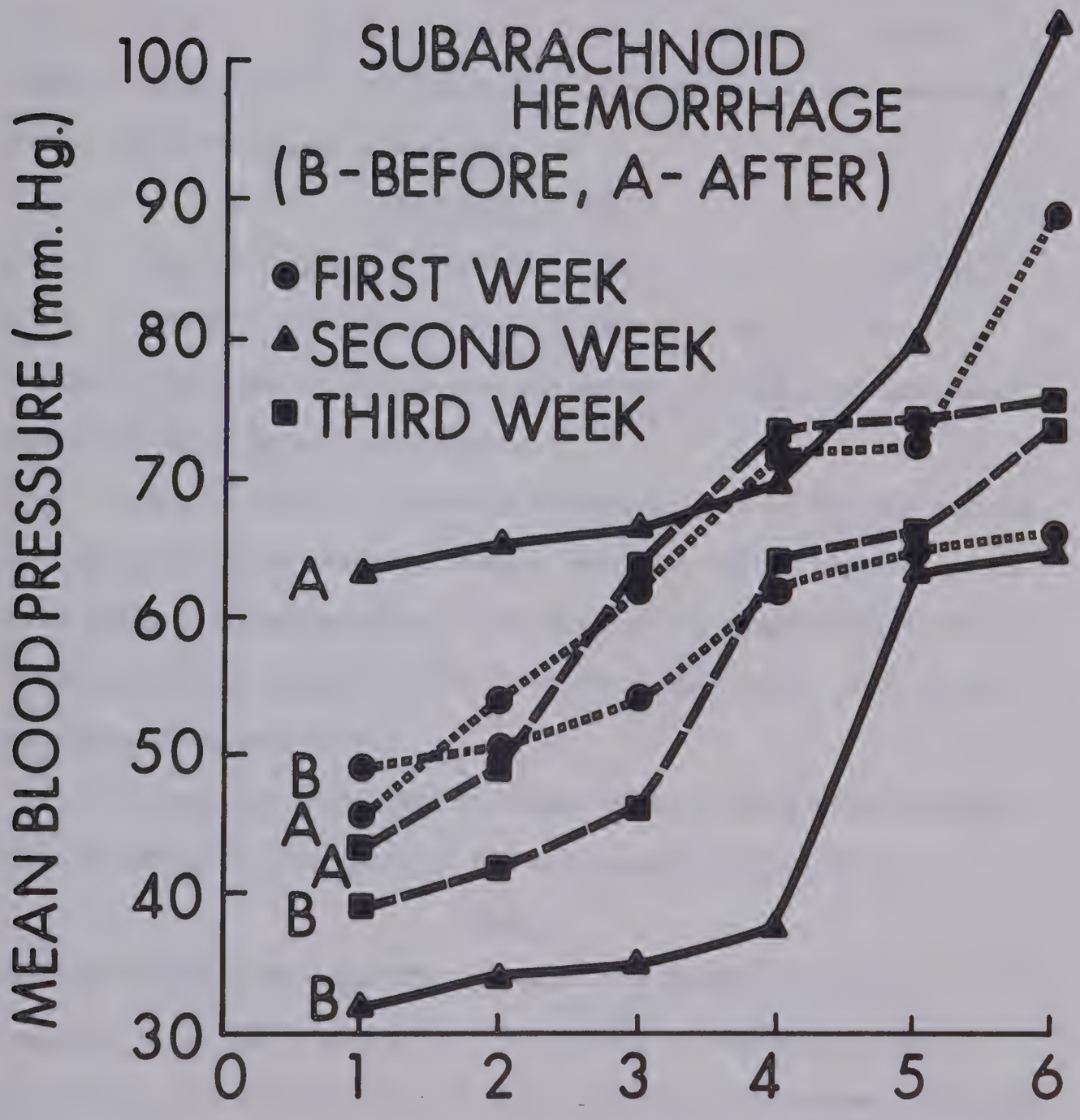
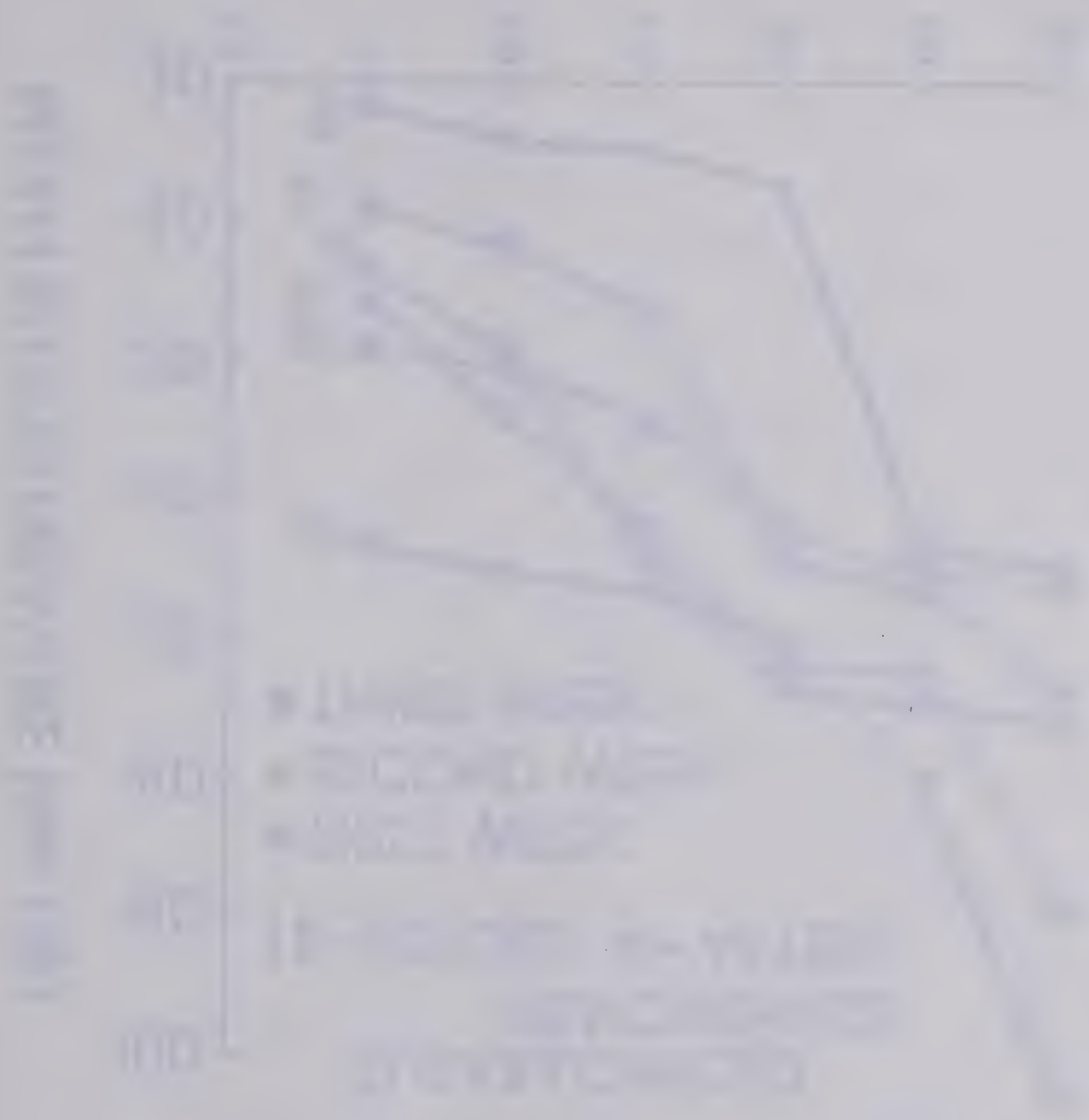

SUBARACHNOID
HEMORRHAGE
(B-BEFORE, A-AFTER)
FIRST WEEK
SECOND WEEK
THIRD WEEK
MEAN BLOOD PRESSURE (mm. Hg.)
100
90
80
70
60
50
40
30
0
1
2
3
4
5
6
A
B
A
A
B
B

FIGURE 13



Comment: There was no significant difference of mean blood pressures before and after second arteriogram.

Week II (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
62.05	41.89	11.03	8.09	10	3.295	0.004

Comment: There was a significant difference of mean blood pressures before and after second arteriogram.

Week III (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
57.88	46.33	14.62	13.41	10	1.302	0.111

Comment: There was no significant difference of mean blood pressures before and after second arteriogram.

Figure 14 shows a cumulative frequency graph of the six animals indicating the blood pressure changes after the second arteriogram in three weeks of experimentation. In spite of the graphic representation of blood pressure changes in the first and third weeks, this was not statistically significant.

D. Analyses of degrees of change of mean blood pressures after first arteriogram, induction of SAH and second arteriogram.

Week I

ADJUSTED ANALYSIS OF VARIANCE - ADJUSTED F = 10.234 P = 0.002

Comment: There was a significant difference of degree of change of mean blood pressures immediately after the first arteriogram, induction of SAH and second arteriogram.

ADJUSTED MEANS

After first arteriogram - 47.51 mm. Hg

After SAH - 68.96 mm. Hg

After second arteriogram - 48.68 mm. Hg

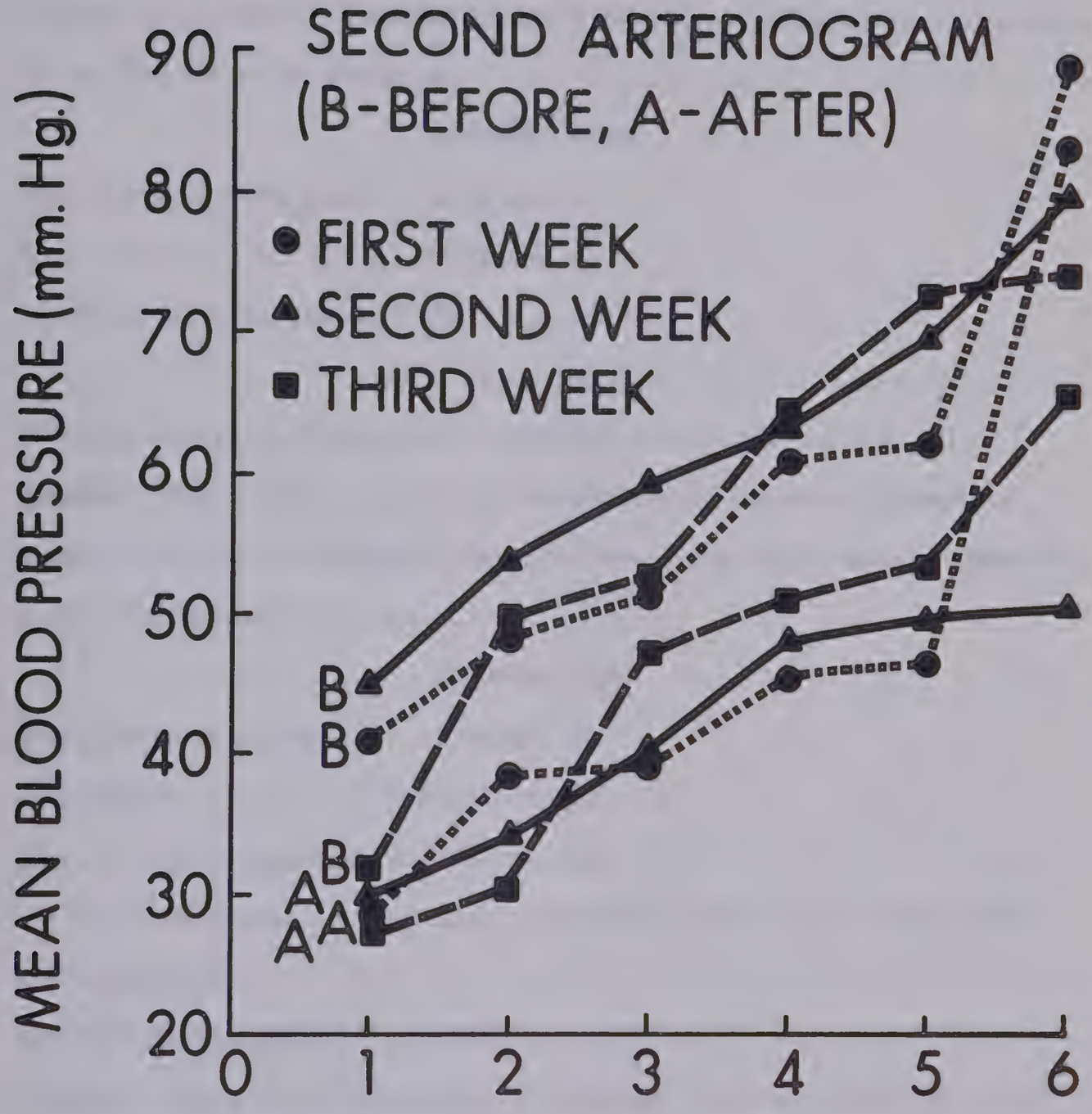

SECOND ARTERIOGRAM
(B-BEFORE, A-AFTER)
FIRST WEEK
SECOND WEEK
THIRD WEEK
MEAN BLOOD PRESSURE (mm. Hg.)
90
80
70
60
50
40
30
20
0
1
2
3
4
5
6
B
B
B
A
A
A

FIGURE 14

Week II

ADJUSTED ANALYSIS OF VARIANCE - ADJUSTED F = 27.099 P = 0.000

Comment: There was a significant difference of degree of change of mean blood pressures immediately after the first arteriogram, induction of SAH and second arteriogram.

ADJUSTED MEANS

After first arteriogram - 33.08 mm. Hg

After SAH - 76.82 mm. Hg

After second arteriogram - 40.08 mm. Hg

Week III

ADJUSTED ANALYSIS OF VARIANCE - ADJUSTED F = 10.452 P = 0.002

Comment: There was a significant difference of degree of change of mean blood pressures immediately after the first arteriogram, induction of SAH and second arteriogram.

ADJUSTED MEANS

After first arteriogram - 41.24 mm. Hg

After SAH - 65.41 mm. Hg

After second arteriogram - 46.60 mm. Hg

E. Analysis of mean blood pressures before first arteriogram over three weeks.

ANALYSIS OF VARIANCE F = 0.336 P = 0.720

Comment: There was no significant difference of mean blood pressures before first arteriogram over three weeks.

F. Analysis of mean blood pressures after first arteriogram over three weeks.

ANALYSIS OF VARIANCE F = 0.401 P = 0.040

Comment: There was a significant difference of mean blood pressures after first arteriogram over three weeks.

G. Analysis of degrees of change of mean blood pressures after first arteriogram over three weeks.

ADJUSTED ANALYSIS OF VARIANCE - ADJUSTED F = 6.533 P = 0.010

Comment: There was a significant difference of degree of change of mean blood pressures after first arteriogram over three weeks.

ADJUSTED MEANS

Week I - 50.03 mm. Hg

Week II - 35.96 mm. Hg

Week III - 43.54 mm. Hg

H. Analysis of mean blood pressures before induction of SAH over three weeks.

ANALYSIS OF VARIANCE F = 1.706 P = 0.215

Comment: There was no significant difference of mean blood pressures before induction of SAH over three weeks.

I. Analysis of mean blood pressures after induction of SAH over three weeks.

ANALYSIS OF VARIANCE F = 0.203 P = 0.818

Comment: There was no significant difference of mean blood pressures after induction of SAH over three weeks.

J. Analysis of degrees of change of mean blood pressures after induction of SAH over three weeks.

ADJUSTED ANALYSIS OF VARIANCE - ADJUSTED F = 5.863 P = 0.943

Comment: There was no significant difference of degree of change of mean blood pressures after induction of SAH over three weeks.

K. Analysis of mean blood pressures before second arteriogram over three weeks.

ANALYSIS OF VARIANCE F = 0.122 P = 0.886

Comment: There was no significant difference of mean blood pressures

before second arteriograms over three weeks.

L. Analysis of mean blood pressures after second arteriogram over three weeks.

ANALYSIS OF VARIANCE F = 0.195 P = 0.824

Comment: There was no significant difference of mean blood pressures after second arteriogram over three weeks.

M. Analysis of degrees of change of mean blood pressures after second arteriogram over three weeks.

ADJUSTED ANALYSIS OF VARIANCE - ADJUSTED F = 1.233 P = 0.321

Comment: There was no significant difference of degree of change of mean blood pressures after second arteriogram over three weeks.

Heart Rates

Recordings of heart rates were made before and after first arteriogram, induction of SAH and second arteriogram.

A. Analyses of heart rates before and after first arteriogram.

Week I (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
123.33	118.33	12.47	10.67	10	0.681	0.255

Comment: There was no significant difference of heart rates before and after first arteriogram.

Week II (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
120.00	106.67	11.55	9.43	10	2.00	0.036

Comment: There was a significant difference of heart rates before and after first arteriogram.

Week III (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
115.00	111.67	19.79	19.51	10	0.268	0.396

Comment: There was no significant difference of heart rates before and after first arteriogram.

B. Analysis of heart rates before and after induction of SAH.

Week I (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
116.67	121.67	13.74	14.62	10	-0.557	0.294

Comment: There was no significant difference of heart rates before and after induction of SAH.

Week II (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
105.00	136.67	9.57	24.27	10	-2.714	0.010

Comment: There was a significant difference of heart rates before and after induction of SAH.

Week III (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
106.67	113.33	17.95	17.95	10	-0.587	0.285

Comment: There was no significant difference of heart rates before and after induction of SAH.

C. Analyses of heart rates before and after second arteriogram.

Week I (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
108.33	103.33	6.87	7.45	10	1.103	0.147

Comment: There was no significant difference of heart rates before and after second arteriogram.

Week II (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
123.33	118.33	27.49	24.09	10	0.306	0.382

Comment: There was no significant difference of heart rates before and

after second arteriogram.

Week III (T - TEST)

XBAR1	XBAR2	SDEV1	SDEV2	DF	T	P-one tail
110.00	108.33	23.09	25.44	10	0.108	0.457

Comment: There was no significant difference of heart rates before and after second arteriogram.

Figure 15 shows cumulative frequency graphs of the six animals indicating heart rate changes after first arteriogram, induction of SAH and second arteriogram in three weeks of experimentation.

D. Analyses of degrees of change of heart rates after first arteriogram, induction of SAH and second arteriogram.

Week I

ADJUSTED ANALYSIS OF VARIANCE - ADJUSTED F = 2.540 P = 0.114

Comment: There was no significant difference of degree of change of heart rates immediately after first arteriogram, induction of SAH and second arteriogram.

Week II

ADJUSTED ANALYSIS OF VARIANCE - ADJUSTED F = 5.271 P = 0.015

Comment: There was a significant difference of degree of change of heart rates immediately after the first arteriogram, induction of SAH and second arteriogram.

ADJUSTED MEANS

After first arteriogram - 104.26/min.

After SAH - 143.52/min.

After second arteriogram - 113.87/min.

Week III

ADJUSTED ANALYSIS OF VARIANCE - ADJUSTED F = 1.653 P = 0.227

Comment: There was no significant difference of degree of change of

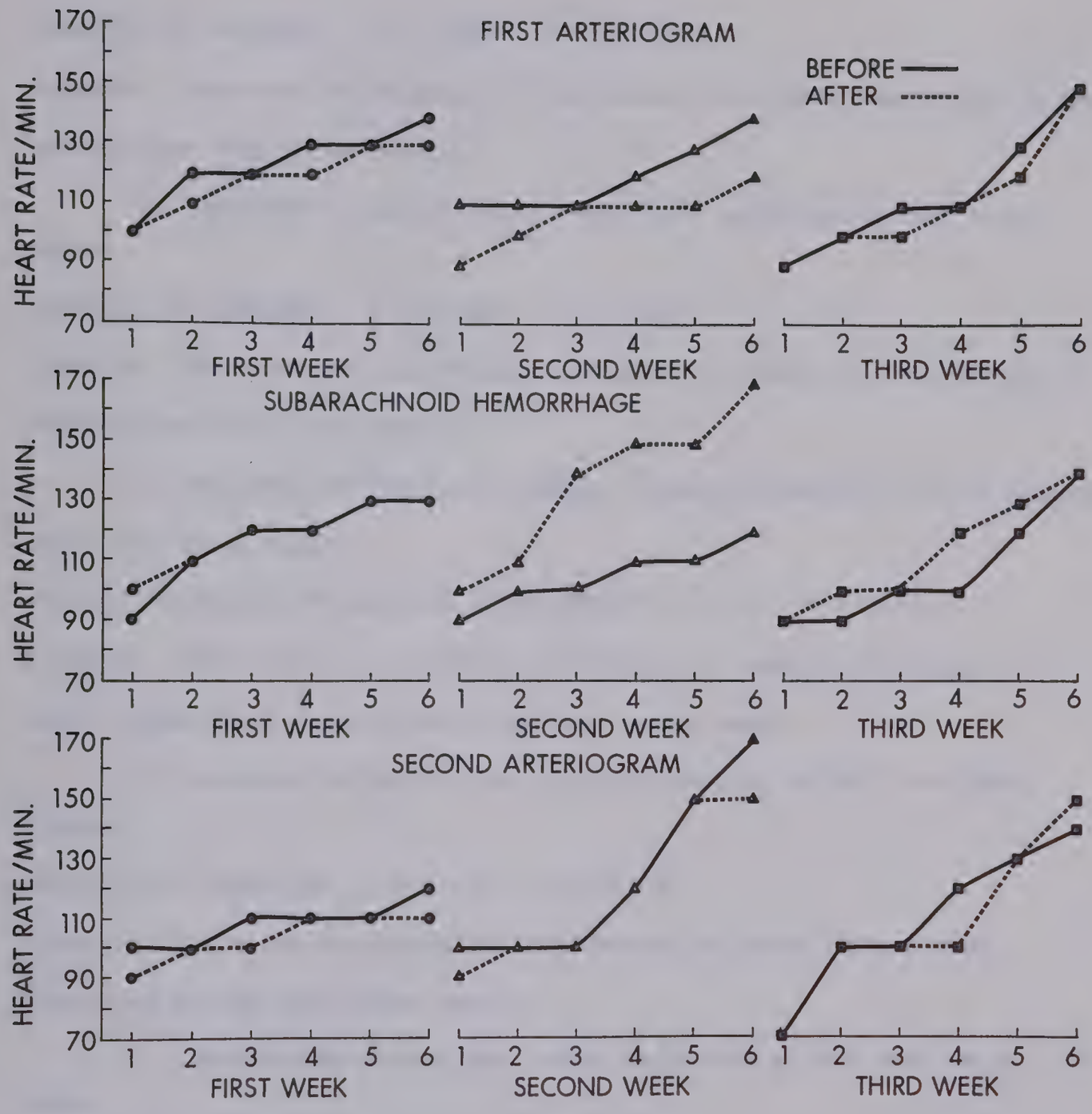

FIRST ARTERIOGRAM
BEFORE
AFTER
HEART RATE/MIN.
170
150
130
110
90
70
1 2 3 4 5 6
FIRST WEEK
SECOND WEEK
THIRD WEEK
SUBARACHNOID HEMORRHAGE
SECOND ARTERIOGRAM

FIGURE 15

heart rates immediately after first arteriogram, induction of SAH and second arteriogram.

E. Analysis of heart rates before first arteriogram over three weeks.

ANALYSIS OF VARIANCE F = 0.387 P = 0.685

Comment: There was no significant difference of heart rates before first arteriogram over three weeks.

F. Analysis of heart rates after first arteriogram over three weeks.

ANALYSIS OF VARIANCE F = 0.880 P = 0.435

Comment: There was no significant difference of heart rates after first arteriogram over three weeks.

G. Analysis of degree of change of heart rates after first arteriogram over three weeks.

ADJUSTED ANALYSIS OF VARIANCE - ADJUSTED F = 2.217 P = 0.146

Comment: There was no significant difference of degree of change of heart rates after first arteriogram over three weeks.

H. Analysis of heart rates before induction of SAH over three weeks.

ANALYSIS OF VARIANCE F = 0.990 P = 0.394

Comment: There was no significant difference of heart rates before induction of SAH over three weeks.

I. Analysis of heart rates after induction of SAH over three weeks.

ANALYSIS OF VARIANCE F = 1.864 P = 0.189

Comment: There was no significant difference of heart rates after induction of SAH over three weeks.

J. Analysis of degrees of change of heart rates after induction of SAH over three weeks.

ADJUSTED ANALYSIS OF VARIANCE - ADJUSTED F = 4.286 P = 0.035

Comment: There was a significant difference of degree of change of heart rates after induction of SAH over three weeks.

ADJUSTED MEANS

Week I - 115.27/min.

Week II - 140.59/min.

Week III - 115.79/min.

K. Analysis of heart rates before second arteriogram over three weeks.

ANALYSIS OF VARIANCE F = 0.758 P = 0.485

Comment: There was no significant difference of heart rates before second arteriogram over three weeks.

L. Analysis of heart rates after second arteriogram over three weeks.

ANALYSIS OF VARIANCE F = 0.681 P = 0.521

Comment: There was no significant difference of heart rates after second arteriogram over three weeks.

M. Analysis of degrees of change of heart rates after second arteriogram over three weeks.

ADJUSTED ANALYSIS OF VARIANCE - ADJUSTED F = 0.120 P = 0.887

Comment: There was no significant difference of degree of change of heart rates after second arteriogram over three weeks.

Electrocardiographic Findings

Monkey 1 has non-specific ST changes after the first induction of subarachnoid hemorrhage. This was not observed in the follow-up EKG done a week later.

Monkey 2 had ventricular arrhythmia after the first induction of subarachnoid hemorrhage. This did not persist in the second EKG done a week later. The second induction caused its reappearance accompanied by

another type of arrhythmia. Both ventricular and supraventricular arrhythmias were observed to persist after the third induction of subarachnoid hemorrhage.

Monkey 3 had ventricular arrhythmia after the first induction of subarachnoid hemorrhage. This was observed to persist in two weekly EKG's. After the third induction, the ventricular arrhythmia disappeared and was replaced by a supraventricular type.

Moneky 4 had a ventricular type of arrhythmia after the second induction of subarachnoid hemorrhage. This did not persist in the follow-up EKG.

Monkey 5 had no evidence of EKG abnormalities during the weekly induction of subarachnoid hemorrhage.

Monkey 6 had a ventricular type of arrhythmia after the second induction of subarachnoid hemorrhage. This did not persist on follow-up EKG done a week later.

CHAPTER VII

DISCUSSION

DISCUSSION

1. Experimental Techniques.

Rhesus monkeys proved to be satisfactory subjects for the observation of cerebral arterial spasm because the gross blood supply of the neck and brain of these animals differs very little from that of man. In the neck, the striking anatomical difference between the two is that in monkeys, both common carotid arteries originate from the brachiocephalic artery [7] (Figure 1). Intracranially, the Circle of Willis closely resembles that of man, except for the formation of the anterior portion. In monkeys, the anterior communicating artery is not a distinct segment. The right and left anterior cerebral arteries unite in the midline to form a single pericallosal artery. These anatomical differences facilitated the observation of vasospasm with less likelihood of misinterpretation. Superimposition of symmetrical vessels was minimized, as was the case in the single pericallosal artery.

Administration of pentobarbital sodium intraperitoneally permitted handling of the subjects and certain procedures which do not need deeper anesthesia, such as lumbar puncture and catheterization. Endotracheal anesthesia and artificial ventilation provided, among other things, constant level of blood gases throughout the length of the procedures. Pre-anesthetic and anesthetic requirements decreased as the subjects underwent repeated experiments. This could be attributed to loss of weight and altered hemostatic mechanism.

The femoral artery was sufficiently large for the introduction of a catheter for arteriography. Problems were encountered only when the artery was unnecessarily irritated, resulting in vasospasm.

Catheterization was quite difficult. Alternate sites for catheterization in the upper extremities were not ideal. Catheterization of the axillary artery was associated with a greater degree of failure and in one instance, gangrene of the extremity. Total ligation of the two femoral arteries, one after the other at weekly intervals, did not produce signs of circulatory deficiency in the lower extremities. With this surgical technique, no significant operative complications or postoperative infection were noted. Introduction and proper placement of the femoral catheter were greatly facilitated by utilizing siliconized catheters and the occasional use of guide wires.

The use of physiologic saline solution with aqueous heparin sodium was adequate to keep the femoral catheter patent during the entire duration of the procedures. Neither operative nor postoperative hemorrhage were encountered with the use of this solution at any time. Retrograde femoral arteriography appeared to be a very satisfactory way of visualizing the cerebral circulation. Preferential filling of either carotid system was also possible. Eight cc. of 60% meglumine iothalamate, injected with a pressure injector at 400 psi, produced a satisfactory opacification of the cerebral vasculature. The use of a total of 20 cc. of this contrast medium in weekly experiments did not produce significant adverse effects on the subjects.

Although biplane arteriography was used, only the lateral projection was utilized for actual measurement of the diameters of the arteries, before and after induction of SAH. In the true lateral view, the proximal segment of the pericallosal artery was delineated adequately. This is due to the fact that superimposition of surrounding structures was minimized. The antero-posterior views were used mainly to verify the existence of vasospasm. The use of a satisfactory monkey holder as

advocated by Ryan et al. [103] has been indispensable for maintaining proper radiographic positions and magnification factors.

Induction of SAH, by injection of autogenous arterial blood through a twist drill hole in the frontal area, was successful. Post mortem examination showed that injected blood circulated in the subarachnoid space into the areas where the arteries under observation were located.

One subject, that had three SAH before post mortem examination, demonstrated signs of recent and old hemorrhages in the leptomeninges. These changes were observed anteriorly in the inferior surfaces of the orbital lobes and posteriorly in the pontine and ambient cisterns. With these findings, it is assumed that the observed arteries were in direct contact with the injected blood.

Introduction of a short bevelled needle in the frontal area above the nasion showed little evidence of parenchymal damage. Infarction around the needle was observed occasionally in the tips of the frontal lobes. This could be attributed to the shape of the frontal lobes of the monkeys. The anterior pole of the frontal lobe is comparatively pointed and its basal surface is concave. The needle sometimes penetrated the undersurface of the frontal lobes as it was inserted.

2. Evidence of Cerebral Vasospasm.

The subjects were analyzed individually to determine whether or not they showed cerebral arterial responses to induced subarachnoid hemorrhage. A subject was considered to exhibit vasospasm if there was diminution of blood vessel diameter in one or both of the two arteries observed.

It has been claimed by Forbes et al. [36] that cerebral arteries can constrict 8 - 10% by reflex stimulation of the sympathetic innerva-

tion. Injected blood might elicit reflex constriction by stimulating the sympathetic innervation of these arteries. How much this mechanism really contributes to the total response is still debatable. The effects seem limited for the following reasons:

A. Electron microscopic observations in intracranial arteries, while they demonstrate structures resembling digital tactile organs, fail to prove the existence of afferent terminals in arterial vessel wall.

B. No specific nerve endings were demonstrated in the tunica media or tunica intima [23].

C. The actual responses of the basal arteries of the brain to experimental sympathetic stimulation were equivocal [71,75,119].

In the present study it was demonstrated that cerebral arterial spasm occurred in all of the three weeks of induced SAH (Week I, P = 0.065; Week II, P = 0.000; Week III, P = 0.042, Figure 7)

The change in the blood vessel diameters after SAH in Week I was considered significant even though it did not quite reach the set confidence level. This is due to the facts that:

A. The sample size is too small to completely reject this borderline change.

B. Comparison of measurements of vessel diameters before and after SAH showed no significant difference from those which exhibited distinct vasospasm.

C. The effect of SAH in the three weeks of induction showed no significant difference of degree of vasospasm.

The other results of the analyses were the following:

A. The diameter of each of the two observed arteries before SAH did not vary over the three weeks (P = 0.535, P = 0.670).

B. The diameter of each of the two observed arteries after SAH

did not vary over the three weeks (P = 0.987, P = 0.811).

C. The degree of vasospasm of each of the two observed arteries did not vary over the three weeks (P = 0.818, P = 0.620).

D. The degree of vasospasm did not vary between the two observed arteries over the three weeks (P = 0.866, P = 0.862, P = 0.991).

These findings clearly indicate that the introduction of fresh arterial blood into the area anterior to the tuberculum sella produces vasospasm in both observed arteries (Figures 8, 9, 10 and 11).

3. Pathogenesis of Cerebral Vasospasm.

The cause and sequence of events leading to this vasospastic response can only be speculated upon. It was obvious that blood introduced into the subarachnoid space circulated to adjacent areas where it came into direct contact with the two observed arteries. This circulation of injected blood through the subarachnoid space was shown by the pathological findings of old and recent hemorrhages in the leptomeninges in animals sacrificed after induction of SAH. Furthermore, injected blood was recovered in the lumbar puncture needle, indicating that it followed the pathways of CSF circulation. As injected blood circulates, it dissects through the subarachnoid space displacing and stretching the arteries or pulling on attached arachnoid bands. This process has been pointed out by Johnson et al. [60] as a possible mechanical cause of vasospasm. As blood comes in direct contact with the external vessel wall, it is possible that the mere physical contact could trigger a vasospastic response. In addition, the various constituents of blood could have elicited a major response. The distinction between mechanical and chemical responses is theoretically possible. The individual effects of these two stimuli could be evaluated if the vasoactive substances were identified and the mechanical effects of blood could be gauged after

successive elimination of these substances. At present, identification of these vasoactive substances has not been accomplished [65].

Inasmuch as measurements of arterial diameters were done 5 - 10 minutes after SAH, it is of interest to speculate on those factors which could produce vasospasm at this early period. Kapp et al. [63] observed the mechanically elicited vasospasm to last about 5 minutes and range in degree from 0 - 48%, with an average of 25% of control diameter. The physical presence of blood could have the same effect as light stroking with a cotton pledget, which these investigators used.

Circulating vasoactive substances should also be considered. Included in this group are epinephrine, norepinephrine, histamine, bradykinin, angiotensin and serotonin. Only angiotensin and serotonin have been found to cause significant vasoconstriction when topically applied [9,63,97,124].

Wilkins et al. [124] found that the normal blood values of catecholamines, angiotensin and serotonin are at or below the level at which minimum sensitivity was observed in spirally cut strips of rabbit aorta. This may indicate that if chemical stimuli alone can produce a significant degree of vasospasm, either the vasoactive substances potentiate one another's effects or another unidentified substance or substances is present. Angiotensin, although it could not be eliminated entirely from consideration in the production of spasm, has been shown to be rapidly destroyed by angiotensinases in the blood and its continued presence in blood clots or bloody cerebrospinal fluid therefore seems unlikely [65]. Serotonin, on the other hand, appears to be a more important factor in influencing the arterial response to SAH. Although it is rapidly oxidized to 5-hydroxyindoleacetic acid, its ability to produce vasospasm is longer-acting than that of angiotensin. This strong vaso-

constrictor agent is released from platelets with the clotting of blood and has been shown to be completely liberated within 15 minutes [9].

Gauging from the degree of vasoconstriction produced by different vasoactive substances, angiotensin and serotonin have been singled out to have profound effect on arterial wall, but neither of these substances consistently produces constriction of the magnitude produced by autogenous blood [64]. This suggests that vasospasm produced by introduction of blood, as in this study, is not primarily caused by a single factor but by combination of at least two, that of mechanical and chemical stimulation. Other unidentified factors are still strongly suspected.

In the present study, weekly induction of SAH did not enhance the production nor the duration of vasospasm. In fact, the arteries fully regained control diameters before the start of succeeding experiments. The exact duration of vasospasm could not be determined because follow-up arteriograms were done only at weekly intervals. Other investigators have shown that it lasts from a few minutes to an hour [9,63,73,111].

Changes in arterial diameter and the overall effects of blood on the cerebral arteries did not differ over the three weeks of induction of SAH. This indicates that the whole sequence of events leading to vasospasm progressed without any residual effects. It is likely that vasoactive substances were liberated with the introduction of blood, that they exerted a brief action on the arterial wall and finally were completely metabolized, leaving the intact artery ready to react again to a similar stimulus.

The absence of evidence of prolonged spasm in the observed arteries showed, among other things, that the tip of the needle used for injection of blood did not puncture either of the two arteries or its adjacent segments. It has been shown by Simeone et al. [111] and Landau et al.

[72] that actual puncturing of blood vessel wall produced prolonged vasospasm lasting from 4 - 7 days. Vasospasm in this case would be an overall response to various factors. These include the following [9]:

A. Reduction in peripheral resistance with the escape of blood from the arterial tree during the actual hemorrhage might cause a local reduction in arterial pressure and thereby cause passive reduction in size of the artery.

B. Local mechanical distortion of arteries may also cause constriction of the vessel. This is considered to be a major contributing factor in the production of acute spasm.

C. Serotonin released from platelets with clotting of blood and other circulating vasoconstrictor agents may be involved.

D. An unknown fraction which is highly spasmogenic, yielded by centrifugation of platelets may be a major factor in prolonged vasospasm [65].

The technique of the present study simulated only the effects of blood extravasated in a particular area and not the effects of disruption of the arterial wall.

4. Direct Effects of Experimental Variables on Blood Vessel Diameter.

It was the aim of the present study to maintain these experimental variables within as narrow a range as possible so that vasospastic responses could be evaluated principally in terms of the effect of subarachnoid blood. However, small changes could not be avoided. Six experimental variables were then measured and analyzed to determine theoretically the degree of influence they could have exerted on the developing vasospasm. The nature of the influence of each of these variables was expressed as a trend towards either vasoconstriction or vasodilation. The real significance of these factors could not be statistically proven

because of the relatively small numbers of observations.

A. pCO_2: pCO_2 values during the first and second arteriograms did not differ significantly over the three weeks of experimentation. In Week I, the mean pCO_2 was 51.41 mm. Hg during the first arteriogram and 47.33 mm. Hg during the second. The effect of increased pCO_2 on the supraclinoid segment of the right carotid artery was such that it tended to dilate the artery, changing its P value from P = 0.065 to P = 0.173. The same effect was observed on the proximal segment of the pericallosal artery (P = 0.251 to P = 0.344). In Week II, mean pCO_2 values were 45.91 mm. Hg and 46.48 mm. Hg during the two arteriographic procedures. The effect of this change on the two arteries was towards vasodilation. In Week III, there was a slight decrease of pCO_2 from the control value. The two arteries tend to constrict with this change (47.66 mm. Hg to 44.0 mm. Hg).

The above observations indicated that pCO_2 values higher than 45 mm. Hg tend to dilate, while lower values tend to constrict cerebral arteries. As has been pointed out, small changes leading to values lower than control still produce a tendency towards vasodilation if the second value remained above the indicated borderline. This critical pCO_2 level, at which the contrasting arterial response diverged, is debatable because it is within normal limits. The tendency towards vasoconstriction below this level could probably be explained by the fact that the coexisting pO_2 was significantly higher than normal. Higher values of pO_2 have been shown [114] to cause slight to moderate cerebral arterial constriction.

B. pH: The range of mean pH values was from 7.331 to 7.411 during the three weeks of induction of SAH. The degrees of change during the first and second arteriograms were correlated with the degrees of arterial

constriction. In Week I, the two arteries differed in their responses; the supraclinoid segment of the internal carotid artery tended to constrict while the proximal segment of the pericallosal artery tended to dilate, as the pH decreased from 7.35 to 7.33. In Weeks II and III, the observed mean pH was slightly lower than the control (7.38 to 7.35; 7.41 to 7.40). The two arteries both showed tendencies toward vasodilation in these two periods. The above observations indicate that pH of 7.33 and lower tends to produce vasoconstriction, while higher values have the opposite effect. Decreasing pH level is well known to produce vasoconstriction in cerebral arteries [114]. The critical levels at which arterial response become evident vary and most likely are influenced by other blood gases.

C. pO_2: The employed method of artificial ventilation produced in the subjects pO_2 levels 3 to 3.5 times higher than normal. These hypersaturated states were maintained throughout the weekly procedures. The mean pO_2 ranged from 298.50 mm. Hg to 356.66 mm. Hg.

In Week I, when the mean pO_2 level increased above the control, the two arteries showed contrasting tendencies. The supraclinoid segment of the right internal carotid artery tended to dilate, while the proximal segment of the pericallosal artery tended to constrict. In Weeks II and III, vasodilation was the trend in both arteries as the observed mean pO_2 increased. With the proximal segment of the pericallosal artery, the pO_2 effect was enough to change its P value from 0.042 to 0.073. These observations are entirely in contrast to what is expected of conditions with pO_2 level exceeding 3 to 3.5 times the normal. Elevated pO_2 produces cerebral vasoconstriction, although of slight to moderate degree [114]. This unexpected result cannot be explained, but a possibility to be considered is that a combination of high oxygen and high carbon dioxide concentrations is associated with almost the same degree

of augmentation of the cerebral blood flow as obtained with increased carbon dioxide alone [114]. The pCO_2 level of the subjects was not extremely high, but was maintained at a slightly elevated value by artificial ventilation. It has been shown here that the pCO_2 effect tends to dilate the arteries.

D. Temperature: Artificial methods of controlling body temperature of subjects during the experimental procedures were not employed. The subjects did not maintain body temperature in spite of the fact that investigations were done at room temperature. Moderate hypothermia was observed in these subjects, with mean temperatures ranging from 32.79°C. to 34.54°C.

In Week I, the two arteries tended to dilate as the temperature dropped from 34.54°C. to 33.33°C.; in Week II, the two arteries tended to dilate as the temperature dropped from 33.34°C. to 32.79°C.; in Week III, the supraclinoid segment of the right internal carotid artery was not influenced by the change of temperature from 33.40°C. to 33.05°C., while the proximal pericallosal artery showed tendency towards dilation.

These responses of the arteries to change of temperature were not consistent over the three weeks and no significance could be attached to them. This does not necessarily eliminate the effects of temperature as a significant factor in the production of vasospasm. Allcock at al. [1] and Kapp et al. [63] have shown both clinically and experimentally that a very low temperature is a predisposing factor to the occurence of cerebral vasospasm.

E. Blood Pressure: No significant difference was observed between the mean blood pressures taken before the first and second arteriograms. It appeared that blood pressure in this particular case had no distinct influence on the vasospastic responses of the observed arteries

at any time.

F. CSF Pressure: In most of the subjects, the injection of blood produced a rise in CSF pressure generally exceeding the mean systemic arterial pressure for less than 10 seconds. A significant increase of CSF pressure lasted only for a few minutes.

Second cerebral arteriograms were usually taken at the time the elevated CSF pressures started declining. The first or control arteriograms, on the other hand, were taken when the CSF pressures were normal. CSF pressure differences during the two procedures were statistically significant in Weeks I and II only ($P = 0.051$, $P = 0.038$, $P = 0.219$).

These findings may indicate that the increased intracranial pressure produced a cuffing effect on the cerebral arteries. Theoretically, this could aggravate the vasospastic responses to subarachnoid blood, but this did not appear to be the case. The time during which the second arteriograms were taken corresponded to the instance when sudden restoration of cerebral flow occurred. The restoration of blood flow was secondary to the rapid decline of CSF pressure. Return of original vessel diameter was presumed in view of the fact that normal circulation was restored with a comparatively higher blood pressure. The increased blood pressure was part of the developing Cushing phenomenon, which was proven to have occurred. Investigation done by Hedges et al. [50] supports the contention that a Cushing phenomenon is necessary for an immediate and rapid restoration of arterial circulation after release of experimentally elevated CSF pressure. Furthermore, the cuffing effect produced an initial period of stasis resulting in local changes of blood gases. An immediate "reactive hyperaemia" is then produced after the release of CSF pressure [81].

Timing of arteriography, in this particular investigation, is

therefore a major factor in minimizing the influence of increased intracranial pressure on arterial response.

5. Relationships of experimental variables.

A. Blood Pressure and Heart Rate: Over the three weeks, the first arteriogram always caused a fall of mean blood pressure ($P = 0.047$ $P = 0.009$, $P = 0.044$, Figure 12). The second arteriogram caused a fall only in the second week ($P = 0.004$, Figure 14).

The induction of subarachnoid hemorrhage produced different degrees of mean blood pressure changes over the three weeks. The greatest change was observed in the second week when the mean blood pressure rose from 44.88 mm. Hg to 74.32 mm. Hg ($P = 0.003$, Figure 13). The changes in the first and third weeks were not as great as in the second, but were statistically significant when compared to the effects of both the first and second arteriograms. The following are their relative values:

Week I: $P = 0.002$, with adjusted means of 47.50 mm. Hg after first arteriogram, 68.96 mm. Hg after SAH and 48.68 mm. Hg after second arteriogram.

Week III: $P = 0.002$, with adjusted means of 41.24 mm. Hg after first arteriogram, 65.41 mm. Hg after SAH and 46.60 mm. Hg after second arteriogram. The overall findings indicated that the repeated procedures produced a comparatively higher degree of change in the second week. The subjects appeared to develop a degree of tolerance thereafter.

Changes in heart rate secondary to arteriogram and SAH differed from those of the blood pressure. No significant change of heart rate was observed during the first and third weeks after first arteriogram. A distinct fall was noted only after the first arteriogram during the second week ($P = 0.036$, mean heart rate of 120/min. to 106.67/min.). Induction of SAH also produced a change which occurred only in the second

week (P = 0.010, 105/min. to 136.67/min.). Second arteriogram produced no statistically significant change of heart rate (Figure 15).

The change of heart rate after the first arteriogram did not correlate with the change in blood pressure. An increase of heart rate is physiologically expected to occur with a fall of blood pressure. In this case, it appears that both heart rate and blood pressure were depressed after the initial cerebral arteriogram. Relative bradycardia and hypotension were observed several seconds after injection of contrast medium. Return to normal values was noted several minutes later. These findings indicate that aortic arch arteriogram, using 60% meglumine iothalamate at 400 psi, has a definite effect on the cardiovascular system of subjects.

Hilal [53] using mongrel dogs observed similar effects. He classified the hemodynamic changes associated with intracarotid injection of radiopaque medium into two phases. The first hypotensive phase is characterized by bradycardia and marked hypotension starting about 4 seconds after the beginning of injection and reaching the minimum by the 5th and 7th seconds. Recovery to normal occurs by the 12th or 15th second. The second hypotensive phase is characterized by a drop in the blood pressure without bradycardia. It starts 17 seconds after injection and complete recovery takes place after 40 to 53 seconds. The present observations parallel the above changes, although not all phases were identified and recorded. The experimental method did not provide continuous recording during contrast medium injection.

The present data suggest that in the first and third weeks, only the second hypotensive phases were recorded. In the second week, the first and second phases were shown in both of the two arteriographic procedures. This leaves the impression that the subjects were compara-

tively more reactive in the second than either the first or third weeks. The injection of contrast medium during the second week produced a prolonged first hypotensive phase that was recorded several seconds after its commencement. This could not be attributed to either the amount of contrast medium, difference of injection pressure or timing of recording, for these were set up identically in the three weeks of investigation. The exact reason for the difference in reactions is not clear. The two phases of hemodynamic changes secondary to injection of contrast medium did not interfere with the accurate determination of arterial diameters. It has been shown [53] that hypotension during the first phase is the result of bradycardia occurring about 4 seconds after injection. This places the radiographic exposure ahead to at least the middle of the arterial phase before changes in cerebral arteries might start in response to the developing bradycardia. It is known that pial vessels show a passive reduction in diameter when sudden hypotension occurs, while a more sustained drop in the blood pressure results in dilation of these vessels. It seems logical then to assume that accurate measurements of vessel diameters were made at a time when neither vasoconstriction nor vasodilation were exhibited secondary to the hemodynamic effects of contrast medium. Furthermore, the contrast medium used does not have any direct effects on the cerebral arterial wall [53].

The first hypotensive phase has been attributed to the irritating effect of the contrast medium on the receptors in the arch of the aorta and its major tributaries, while the second hypotensive phase to the central effects of the contrast medium on the vasomotor centers [31,43,53].

B. CSF Pressure, Blood Pressure and EKG Changes: The changes in blood pressure after induction of SAH could be attributed to the increase of intracranial pressure and to the central effects of blood on the vaso-

motor centers. This change appeared to be a Cushing phenomenon. The injection of blood produced intracranial pressures higher than the systemic arterial pressure in most of the subjects. Although this possibly contributed to the occurrence of a Cushing phenomenon, this was not necessary since the increased CSF pressure was at or about the mean systemic blood pressure in all subjects [50].

Changes in the heart rate and other EKG abnormalities cannot be explained on the basis of increased CSF pressure alone. Hersch et al. [52] have shown that abnormal EKG tracings were not as frequent in cases with intracranial space-occupying lesions as in cases with subarachnoid hemorrhage.

Aside from changes of heart rate, the arteriographic procedure did not produce any other EKG abnormalities. With induction of SAH, one subject showed no change at all, one had a non-specific ST change and the rest had various types of cardiac arrhythmias. Ventricular and supraventricular arrhythmias appeared to increase in the second week. Two subjects showed these changes in the first week, four in the second and two in the third. The characteristic changes in the first week were similar to the third week.

A number of reports have appeared in the literature describing these EKG changes secondary to intracranial hemorrhage [22,42,87,102,115]. Disturbances of autonomic influences and hypothalamic activity have been singly and jointly cited by several investigators as the cause of these EKG abnormalities. Cropp et al. [22] have suggested that stimulation of the orbital surface of the frontal lobe (area 13) and the anterior cingulate gyrus (area 24) results in a rise or fall in blood pressure, alterations in heart rate and other EKG changes. Pool [87] suggested that the changes are mediated through vasocardiac reflexes. If this is

true, hemorrhage around an artery might trigger these reflexes, causing EKG abnormalities. Greenhoot et al. [42] on the other hand, believe that activation of sympathetic "centers" in the posterior diencephalon and upper midbrain, either by stimulation or by lesions more anteriorly which alter the balance of autonomic outflow, results in sympathetic discharge capable of producing myocardial necrosis. They further proposed that the myocardial necrosis is due to the release of catecholamines from adrenergic nerve endings in the heart.

CHAPTER VIII

SUMMARY

SUMMARY

1. The described method of studying cerebral arterial response to induced subarachnoid hemorrhage in rhesus monkeys was shown to be satisfactory. The presence of a single pericallosal artery in this particular species plus the fact that preferential arteriographic studies of the carotid arterial system were possible, made the observations precise and uncomplicated.

2. The use of endotracheal anesthesia and artificial ventilation have limited the influence of the experimental variables on the arterial response to SAH.

3. Retrograde femoral arteriography appeared to be the most satisfactory way of visualizing the cerebral circulation of rhesus monkeys. This approach was proven to be superior to any technique utilizing the peripheral vasculature.

4. Induction of subarachnoid hemorrhage by injection of autogenous arterial blood into an area anterior to the tuberculum sella was sufficient to insure that blood circulated and came into contact with the supraclinoid segment of the right internal carotid and proximal segment of the pericallosal arteries.

5. Injection of 4 cc. of autogenous arterial blood into the subarachnoid space produced an acute rise of CSF pressure which levelled off to control value after a few minutes. This rise was enough to stimulate an arterial response without producing a prolonged increase of CSF pressure or simulating a mass lesion effect.

6. A technique similar to that applied in man was used to perform lumbar punctures in the subjects. The best results were obtained with the subjects premedicated and supported in a sitting position. This

eliminated the necessity of doing a laminectomy to insure proper lumbar catheterization.

7. Vasospasm was proven statistically to occur in the three weeks of induced SAH. The exact duration of spasm was not fully determined but was observed definitely to last for less than a week. Repeated injections of blood did not influence the degree of vasospasm observed during weekly experiments. No difference of degree of vasospasm was observed between the two arteries over the three weeks.

8. Heart rate and blood pressure were shown to be affected by induction of SAH and by the arteriographic procedures. Blood pressure and heart rate decreased after arteriograms and increased after induction of SAH. Central effects of the contrast medium and subarachnoid blood on the vasomotor centers were discussed as probable causes.

REFERENCES

REFERENCES

1. ALLCOCK, J.M. and DRAKE, C.G. Ruptured intracranial aneurysms: The role of arterial spasm. J. Neurosurg. 22:21-29, 1965.

2. AMES, A. III, WRIGHT, R.L., KOWADA, M., THURSTON, J. and MAJNO, G. Cerebral ischemia. II. The no-reflow phenomenon. Amer. J. Path. 52:437-453, 1968.

3. ATTA, A.G. and VANACE, P.W. Electrocardiographic studies in the macaca mulatta monkey. Ann. N.Y. Acad. Sci. 85, Art. 3:811-818, 1960.

4. BAYLISS, W.M. On the local reactions of the arterial wall to changes of internal pressure. J. Physiol. 28:220-231, 1902.

5. BERNSMEIER, A. and SIEMONS, K. Die messung der hirndurchblutung mit der stick-oxydulmethode. Pflugers Arch. 258:169, 1965.

6. BILLINGLEY, P.R. and RANSON, S.W. Branches of ganglion cervicale superius. J. Comp. Neurol. 29:367-384, 1918.

7. BONAKDARPOUR, A., LYNCH, P.R., LAPAYOWKER, M.S. and STAUFFER, H.M. Arch aortography and cervicocerebral angiography in the rhesus monkey correlated with corrosion cast. Invest. Radiol. 2:432-441, 1967.

8. BOTTERELL, E.H., LOUGHEED, W.M., MORLEY, T.P. and VANDEWATER, S.C. Hypothermia in the surgical treatment of ruptured intracranial aneurysm. J. Neurosurg. 15:4-18, 1958.

9. BRAWLEY, B.W., STRANDNESS, D.E. JR. and KELLEY, W.A. The biphasic response to cerebral vasospasm in experimental subarachnoid hemorrhage. J. Neurosurg. 28:1-8, 1968.

10. BRIDGES, T.J., CLARK, K. and YAHR, M.D. Plethysmographic studies of cerebral circulation: Evidence for cranial nerve vasomotor activity. J. Clin. Invest. 37:363-372, 1958.

11. BRUNTON, T.L. On the pathology and treatment of some forms of headache. St. Barth. Hosp. Rep. 19:329, 1883.

12. BRUNTON, T.L. Observations on functional diseases of the arteries. Lancet 2:161, 1915.

13. BUCKELL, M. Demonstration of substances capable of contracting smooth muscle in the hematoma fluid from certain cases of ruptured cerebral aneurysm. J. Neurol. Neurosurg. Psychiat. 27:198-199, 1964.

14. BUCKELL, M. Biochemical changes after spontaneous subarachnoid haemorrhage. J. Neurol. Neurosurg. Psychiat. 29:291-298, 1966.

15. BUCKLE, R.M., DU BOULAY, G. and SMITH, B. Death due to cerebral vasospasm. J. Neurol. Neurosurg. Psychiat. 27:440-444, 1964.

16. BYROM, F.G. The pathogenesis of hypertensive encephalopathy and its relation to the malignant phase of hypertension. Lancet 2: 201-211, 1954.

17. CANTU, R.C. and AMES, A. III. Experimental prevention of cerebral vasculature obstruction produced by ischemia. J. Neurosurg. 30:50-54, 1969.

18. CARLYLE, A. and GRAYSON, J. Blood pressure and the regulation of brain blood flow. J. Physiol. (London) 127:15P-16P, 1955.

19. CHOROBSKI, J. and PENFIELD, W. Cerebral vasodilator nerves and their pathway from the medulla oblongata with observations on pial and intracerebral vascular plexus. Arch. Neurol. and Psychiat. 28: 1257-1289, 1932.

20. CLARKE, J.A. An x-ray microscopic study of the vasa vasorum of the intracranial arteries. Zeitschrift fur Anatomie und Entwicklungsgeschichte 124:396-400, 1965.

21. CORDAY, E., ROTHENBERG, S.F. and IRVING, D.W. Cerebral angiospasm. A cause of the cerebral stroke. Amer. J. Cardiol. 11:66-71, 1963.

22. CROPP, G.J. and MANNING, G.W. Electrocardiographic changes simulating myocardial ischemia and infarction associated with spontaneous intracranial hemorrhage. Circulation 22:25-38, 1960.

23. DAHL, E. and NELSON, E. Electron microscopic observations on human intracranial arteries. II. Innervation. Arch. Neurol. 10: 158-164, 1964.

24. DU BOULAY, G. Distribution of spasm in the intracranial arteries after subarachnoid hemorrhage. Acta Radiol. Diagn. 1:257-266, 1963.

25. ECHLIN, F.A. Cerebral ischaemia and its relation to epilepsy. (Thesis) Montreal: McGill University, 1939.

26. ECHLIN, F.A. Vasospasm and focal cerebral ischemia. An experimental study. Arch. Neurol. Psychiat. (Chicago) 47:77-96, 1942.

27. ECHLIN, F. Spasm of basilar and vertebral arteries caused by experimental subarachnoid hemorrhage. J. Neurosurg. 23:1-11, 1965.

28. ECKER, A. and RIEMENSCHNEIDER, P.A. Arteriographic demonstration of spasm of the intracranial arteries with special reference to saccular arterial aneurysms. J. Neurosurg. 8:660-667, 1951.

29. EDWARDS, E.A. Anatomy of collateral circulation. Surg. Gynec. Obst. 107:183-194, 1958.

30. EISEN, V. Fibrinolysis and formation of biologically active polypeptides. Brit. Med. Bull. 20:205-209, 1964.

31. EPSTEIN, J.A. and EPSTEIN, B.S. Electrocardiographic alterations observed during percutaneous cerebral angiography. Arch. Neurol. Psychiat. 81:142, 1959.

32. FANG, H.C.H. Cerebral arterial innervations in man. Arch. Neurol. 4:651-656, 1961.

33. FEINDEL, W., GARRETSON, H., YAMAMOTO, Y.L., PEROT, P. and RUMIN, N. Blood flow patterns in the cerebral vessels and cortex in man studied in intra-carotid injection of radioisotopes and coomassie blue dye. J. Neurosurg. 23:12-21, 1965.

34. FLETCHER, T.M., TAVERAS, J.M. and POOL, J.L. Cerebral vasospasm in angiography for intracranial aneurysms. A.M.A. Arch. Neurol. 1: 38-47, 1959.

35. FLOREY, H. Microscopic observations on the circulation of blood in the cerebral cortex. Brain 48:43-64, 1925.

36. FORBES, H.S. and COBB, S. Vasomotor control of cerebral vessels. Res. Publ. Ass. Nerv. Ment. Dis. 18:201-217, 1938.

37. FORBES, H.S. and WOLFF, H.G. Cerebral circulation. III. The vasomotor control of cerebral vessels. Arch. Neurol. Psychiat. (Chicago) 19:1057-1086, 1928.

38. FOX, J.L. Development of recent thoughts on intracranial pressure and the blood-brain barrier. J. Neurosurg. 21:909-947, 1964.

39. GILLINGHAM, F.J. The management of ruptured intracranial aneurysm. Ann. Roy. Coll. Surg. Eng. 23:87-117, 1958.

40. GOODMAN, L.A. Kolmogorov-Smirnov test for psychological research. Psychol. Bull. 51, No. 2:160-168, 1954.

41. GOTOH, F., MEYER, J. and TAKAGI, Y. Cerebral effects of hyperventilation in man. Arch. Neurol. 12:410-423, 1965.

42. GREENHOOT, J.H. and REICHENBACH, D.D. Cardiac injury and subarachnoid hemorrhage. J. Neurosurg. 30:521-531, 1969.

43. GREITZ, T. A radiologic study of brain circulation by rapid serial angiography of the carotid artery. Acta Radiol. Suppl. No. 140, 1956.

44. GREITZ, T. Dilatation of cerebral veins during cerebral angiography with water-soluble contrast media. Acta Radiol. Diagn. 4:625-631, 1966.

45. GURDJIAN, E.S. and THOMAS, L.M. Cinephotomicrography of pial circulation. A study of factors influencing vascular caliber; preliminary report. Arch. Neurol. Psychiat. (Chicago) 80: 418-435, 1958.

46. HARDESTY, W.H., ROBERTS, B., TOOLE, J.F. and ROYSTER, H.P. Studies of carotid artery blood flow in man. New Eng. J. Med. 263:944-946, 1960.

47. HARDESTY, W.H., WENDELL, W.B., TOOLE, J.F., RANDALL, P. and ROYSTER, H.P. Studies on vertebral artery blood flow in man. Surg. Gynec. Obst. 116:662-664, 1963.

48. HARVEY, J. and RASMUSSEN, T. Occlusion of the middle cerebral artery. An experimental study. Arch. Neurol. Psychiat. (Chicago) 66:20-29, 1951.

49. HASEGA, T., RAVENS, J.R. and TOOLE, J.F. Pre-capillary arteriovenous anastomoses. Arch. Neurol. 16:217-224, 1967.

50. HEDGES, T.R. and WEINSTEIN, J.D. Cerebrovascular responses to increased intracranial pressure. J. Neurosurg. 21:292-297, 1964.

51. HEDLUND, S. The hemodynamics of the cerebral blood circulation by means of radioactive isotopes. Acta Neurol. Scand. 41, Suppl. 13 (part I):299-307, 1965.

52. HERSCH, C. Electrocardiographic changes in subarachnoid haemorrhage, meningitis and intracranial space-occupying lesions. Brit. Heart J. 26:785-793, 1964.

53. HILAL, S.K. Hemodynamic changes associated with the intra-arterial injection of contrast media. Radiol. 86:615-633, 1966.

54. HUBER, P. and HANDA, J.J. Effect of contrast material, hypercapnia, hyperventilation, hypertonic glucose and papaverine on the diameter of the cerebral arteries. Invest. Radiol. 2:17-32, 1967.

55. HUDSON, C.H. and RAAF, J. Timing of angiography and operation in patients with ruptured intracranial aneurysms. J. Neurosurg. 29: 37-41, 1968.

56. HUNT, W.E. and HESS, R.M. Surgical risk as related to time of intervention in the repair of intracranial aneurysms. J. Neurosurg. 28:14-20, 1968.

57. HUNT, W.E., MEAGHER, J.N. and BARNES, J.E. The management of intracranial aneurysm. J. Neurosurg. 19:34-40, 1962.

58. ISHIKAWA, S., HANDA, J., MEYER, J. and HUBER, P. Haemodynamics of the circle of Willis and the leptomeningeal anastomosis: An electromagnetic flowmeter study of intracranial arterial occlusion in the monkey. J. Neurol. Neurosurg. Psychiat. 28:124-136, 1965.

59. JANZEN, W. The relationship between the perivascular and the subarachnoid space. Psychiat. Neurol. Neurochir. 64:37-45, 1961.

60. JOHNSON, R.J., POTTER, J.M. and REID, R.G. Arterial spasm in subarachnoid haemorrhage: Mechanical considerations. J. Neurol. Neurosurg. Psychiat. 21:68, 1958.

61. JOYNT, R.J., AFIFI, A. and HARBISON, J. Hyponatremia in subarachnoid hemorrhage. Arch. Neurol. 13:633-638, 1965.

62. KAK, V.K. and TAYLOR, A.R. Cerebral blood flow in subarachnoid haemorrhage. Lancet 1:875-877, 1967.

63. KAPP, J., MAHALEY, M.S., JR. and ODOM, G.L. Cerebral arterial spasm. Part I: Evaluation of experimental variables affecting the diameter of the exposed basilar artery. J. Neurosurg. 29:331-338, 1968.

64. KAPP, J., MAHALEY, M.S., JR. and ODOM, G.L. Cerebral spasm. Part 2: Experimental evaluation of mechanical and humoral factors in pathogenesis. J. Neurosurg. 29:339-349, 1968.

65. KAPP, J., MAHALEY, M.S., JR. and ODOM, G.L. Cerebral spasm. Part 3: Partial purification and characterization of as spasmogenic substance in feline platelets. J. Neurosurg. 29:350-356, 1968.

66. KARLSBERG, P., ELLIOT, H.W. and ADAMS, J.E. Effect of various pharmacologic agents on cerebral arteries. Neurology (Minneap.) 13:772-778, 1963.

67. KETTY, S.S., SHENKIN, H.A. and SCHMIDT, C.F. The effects of increased intracranial pressure on cerebral circulatory functions in man. J. Clin. Invest. 27:493-498, 1948.

68. KINDT, G.W., YOUMANS, J.R. and ALBRAND, O. Factors influencing the autoregulation of the cerebral blood flow during hypotension and hypertension. J. Neurosurg. 26:299-304, 1967.

69. KRIEGER, D.T., KOLODNY, H.D. and WARNER, R.P. Serum serotonin in nervous system disease. Neurology (Minneap.) 14:578-580, 1964.

70. KRISE, G.M. Hematology of the normal monkey. Ann. N.Y. Acad. Sci. 85, Art. 3:803-809, 1960.

71. KROG, J. Autonomic nervous control of the cerebral blood flow in man. J. Oslo City Hosp. 14:25-33, 1964.

72. KUHN, R.A. The speed of cerebral circulation. New Eng. J. Med. 267:689-695, 1962.

73. LANDAU, B. and RANSOHOFF, J. Prolonged cerebral vasospasm in experimental subarachnoid hemorrhage. Neurology (Minneap.) 18:1056-1065, 1968.

74. LASSEN, N.A. Cerebral blood flow and oxygen consumption in man. Physiol. Rev. 39:183-238, 1959.

75. LASSEN, N.A. Autoregulation of cerebral blood flow. Circ. Res., Suppl. I, 14, 15:201-204, 1964.

76. LENDE, R.A. Local spasm in cerebral arteries. J. Neurosurg. 17: 90-103, 1960.

77. LOGUE, V. Surgery in spontaneous subarachnoid haemorrhage: Operative treatment of aneurysms of the anterior cerebral and anterior communicating artery. Brit. Med. J. 1:473-479, 1956.

78. MASPES, P.E. and MARINI, G. Intracranial arterial spasm related to supraclinoid ruptured aneurysms. Acta Neurochir. BD 10: 630-636, 1961.

79. McDONALD, D.A. and POTTER, J.M. The distribution of blood to the brain. J. Physiol. 114:356-371, 1951.

80. MOUNT, L.A. and TAVERAS, J.M. Arteriographic demonstration of collateral circulation of cerebral hemispheres. Arch. Neurol. Psychiat. 78:235-253, 1957.

81. NOELL, W. and SCHNEIDER, M. Zur hamodynamik der gehirndurchblutung bei liquordrucksteigerung. Arch. Psychiat. Nervenkr. 180:713-730, 1948.

82. NORLEN, G. and OLIVECRONA, H. The treatment of aneurysms of the circle of Willis. J. Neurosurg. 10:404-415, 1953.

83. OHTA, T. and BALDWIN, M. Experimental mechanical arterial stimulation at the circle of Willis. J. Neurosurg. 28:405-408, 1968.

84. OLDENDORF, W.H. and DAVSON, H. Brain extracellular space and the sink action of cerebrospinal fluid. Arch. Neurol. 17:196-205, 1967.

85. PENFIELD, W., LENDE, R.A. and RASMUSSEN, T. Manipulation hemiplegia. An untoward complication in the surgery of focal epilepsy. J. Neurosurg. 18:760-776, 1961.

86. PICKERING, G.W. Vascular spasm. Lancet 2:845-850, 1951.

87. POOL, J.L. Vasocardiac effects of the circle of Willis. Arch. Neurol. Psychiat. 78:355-367, 1957.

88. POOL, J.L. Cerebral vasospasm. New Eng. J. Med. 259:1259-1264, 1958.

89. POOL, J.L. Timing and techniques in the intracranial surgery of ruptured aneurysms of the anterior communicating artery. J. Neurosurg. 19:378-388, 1962.

90. POOL, J.L., JACOBSON, S. and FLETCHER, T.A. Cerebral vasospasm: Clinical and experimental evidence. J.A.M.A. 167:1599-1601, 1958.

91. POOL, J.L. and POTTS, D.G. Aneurysms and Arteriovenous Anomalies of the Brain. Hoeber Medical Division, Harper and Row Publishers, 1965.

92. POTTER, J.M. Cerebral arterial spasm: A short review. World Neurology 2:576-584, 1961.

93. POTTER, J.M. Redistribution of blood to the brain due to localized cerebral arterial spasm. Brain 82:367-376, 1961.

94. RAPELA, C.E., MACHOWICZ, P. and GREEN, H.D. Cerebral venous blood flow. Fed. Proc. 20:100, 1961.

95. RASMUSSEN, K.H., SKINHOJ, E., PAULSON, D., EWALD, J., BJERRUM, J.K. FAHRENKRUG, A. and LASSEN, N.A. Regional cerebral blood flow in acute apoplexy. Arch. Neurol. 17:271-281, 1967.

96. RAY, B.S. and WOLFF, H.G. Experimental studies on headache: Pain-sensitive structures of the head and their significance in headache. Arch. Surg. 41:813-856, 1940.

97. RAYNOR, R.B., McMURTRY, J.G. and POOL, J.L. Cerebrovascular effects of topically applied serotonin in the cat. Neurology 11:190-195, 1961.

98. RAYNOR, R.B. and ROSS, G. Arteriography and vasospasm. J. Neurosurg. 17:1055-1061, 1960.

99. ROBERTSON, E.G. Cerebral lesions due to intracranial aneurysms. Brain 72:150-185, 1949.

100. ROWBOTHAM, G.F. and LITTLE, E. A new concept of the circulation and the circulations of the brain. Brit. J. Surg. 52:539-542, 1965.

101. ROY, C.S. and SHERRINGTON, C.S. On the regulation of the blood of the brain. J. Physiol. 11:85, 1890.

102. RUSSELL, A.S. The association of subarachnoid haemorrhage with an abnormal electrocardiogram and acute pulmonary oedema. Guy Hosp. Rep. 115:463-474, 1966.

103. RYAN, K.G., SIMEONE, F.A., CORTESE, D.A. and COTTER, R.J. Cerebral angiography in the rhesus monkey. Invest. Radiol. 4:34-40, 1969.

104. SCHAIN, R.J. Neurohumors and other pharmacologically active substances in cerebrospinal fluid: A review of the literature. Yale J. Biol. Med. 33:15-36, 1960-1961.

105. SCHNECK, S.A. and KRICHEFF, I.I. Intracranial aneurysm rupture, vasospasm and infarction. Arch. Neurol. 11:668-680, 1964.

106. SHALIT, M.N., SHIMOJYO, S. and REINMUTH, O.M. Carbon dioxide and cerebral circulatory control. I. The extravascular effect. Arch. Neurol. 17:298-303, 1967.

107. SHALIT, M.N., SHIMOJYO, S. and REINMUTH, O.M. Carbon dioxide and cerebral circulatory control. II. The intravascular effect. Arch. Neurol. 17:337-341, 1967.

108. SHALIT, M.N., SHIMOJYO, S. and REINMUTH, O.M. Carbon dioxide and cerebral circulatory control. III. The effects of brain stem lesions. Arch. Neurol. 17:342-353, 1967.

109. SHUSTER, S. The electrocardiogram in subarachnoid haemorrhage. Brit. Heart J. 22:316-320, 1960.

110. SIEGEL, S. Nonparametric Statistics for the Behavioral Sciences. McGraw-Hill Book Co., Inc., New York, 1956.

111. SIMEONE, F.A., RYAN, K.G. and COTTER, J.R. Prolonged experimental cerebral vasospasm. J. Neurosurg. 29:357-366, 1968.

112. SMITH, B. Cerebral pathology in subarachnoid haemorrhage. J. Neurol. Neurosurg. Psychiat. 26:535-539, 1963.

113. SOKOLOFF, L. The action of drugs on the cerebral circulation. Pharmacol. Rev. 11:1-86, 1959.

114. SOKOLOFF, L. and KETY, S. Regulation of cerebral circulation. Physiol. Rev. 40, Suppl. 4:38-43, 1960.

115. SRIVASTAVA, S.C. and ROBSON, A.O. Electrocardiographic abnormalities associated with subarachnoid haemorrhage. Lancet 2:431-434, 1964.

116. STORNELLI, S.A. and FRENCH, J.D. Subarachnoid hemorrhage: Factors in prognosis and management. J. Neurosurg. 21:769-779, 1964.

117. UCHIDA, E., BOHR, D.F. and HOOBLER, S.W. A method for studying isolated resistance vessels from rabbit mesentery and brain and their responses to drugs. Circ. Res. 21:525-536, 1967.

118. WALKER, H.M. and LEV, J. Elementary Statistical Methods. Revised Edition. Holt, Rinehart and Winston, New York, 1958.

119. WALTZ, A. Effect of blood pressure on blood flow in ischemic and in nonischemic cerebral cortex. Neurology (Minneap.) 18:613-621, 1968.

120. WEINER, D.E. Measurement of total cerebral blood flow in the monkey by external monitoring of cesium-131. Circ. Res. 21:805-816, 1967.

121. WELLS, C.E. The cerebral circulation: The clinical significance of current concepts. Arch. Neurol. 3:319-331, 1960.

122. WILKINS, R.H., ALEXANDER, J.A. and ODOM, G.L. Intracranial arterial spasm: A clinical analysis. J. Neurosurg. 29:121-134, 1968.

123. WILKINS, R.H., SILVER, D. and ODOM, G.L. The role of circulating substances in intracranial arterial spasm. Neurology (Minneap.) 16:482-490, 1966.

124. WILKINS, R., WILKINS, G., GUNNELS, J.C. and ODOM, G.L. Experimental studies of intracranial arterial spasm using aortic strip assays. J. Neurosurg. 27:490-500, 1961.

125. WILKS, S.S. Elementary Statistical Analysis. Princeton University Press, Princeton, New Jersey, 1951.

126. WINER, B.J. Statistical Principles in Experimental Design. McGraw-Hill Book Co., New York, 1962.

127. WOODBURY, D.M. and KARLER, R. The role of carbon dioxide in the nervous system. Anesthesiology 21:686-701, 1960.

128. ZINGESSER, L.H., SCHECTER, M.M., DEXTER, J., KATZMAN, R. and SCHEINBERG, L.C. On the significance of spasm associated with rupture of a cerebral aneurysm. Arch. Neurol. 18:520-528, 1968.